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Prioritätsbescheinigung über die Einreichung einer Patentanmeldung

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Bezeichnung:	Neue Effektor-Konjugate, Verfahren zu ihrer Herstellung und ihre pharmazeutische Verwendung
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Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

München, den 4. August 2003
Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

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Anmelder: Schering AG
Unser Zeichen: SCH10522DE2

Neue Effektor-Konjugate, Verfahren zu Ihrer Herstellung und Ihre pharmazeutische Verwendung

Die Entwicklung des Verständnisses betreffend die Erkennung von Bindungsregionen, insbesondere auf dem Gebiet der monoklonalen Antikörper oder deren Fragmente gegen spezifische Tumor-Antigene, ermöglicht es, an eine selektive Tumor-Therapie durch gezielte Freisetzung eines Anti-Tumor-Wirkstoffes am Zielort zu denken.

Voraussetzung für einen derartigen Ansatz, bei dem ein hoch aktiver (toxischer) Wirkstoff (Effektor) an eine hochmolekulare Tumor-spezifische Erkennungseinheit wie beispielsweise an einen Antikörper gekuppelt wird, ist eine weitgehende Inaktivität des Konjugates, dessen Mindestbestandteile eine Erkennungseinheit und einen Effektor darstellen, bis dieses den Zielort (Tumor) erreicht hat. Am Zielort angelangt, bindet das Konjugat an der Zelloberfläche und der Wirkstoff kann, gegebenenfalls nach vorangegangener Internalisierung des gesamten Komplexes, freigesetzt werden.

Die erfolgreiche Therapie solider Tumore, insbesondere mit monoklonalen Antikörpern, kann jedoch eingeschränkt werden durch eine unzureichende Penetration des Antikörpers in den Tumor sowie die heterogene Verteilung des entsprechenden tumorassoziierten Antigens im Tumorgewebe.

Diese Einschränkungen könnten dadurch umgangen werden, dass man in spezifischer Weise das Tumor-Gefäßsystem angreift. Das Wachstum von Tumoren unterhalb eines Volumens von etwa 2 mm^3 ist abhängig von einer Neoangiogenese. Das weitere Tumorwachstum basiert auf einem intakten Gefäßsystem, das die Versorgung mit Nährstoffen bzw. Entsorgung von

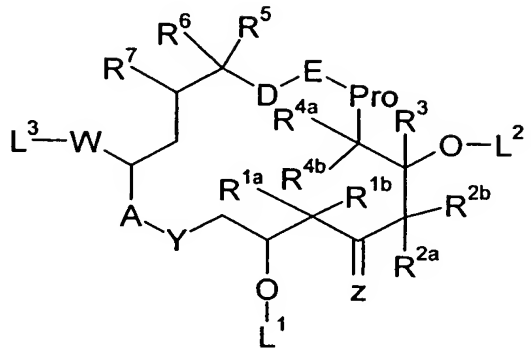
Abfallprodukten gewährleistet. Die selektive Zerstörung dieses Systems sollte deshalb zu einem Absterben des Tumors führen. Der Angriff auf das Gefäßsystem des Tumors verspricht gegenüber dem direkten Angriff auf den Tumor selbst eine Reihe von Vorteilen. Im Vergleich zu Tumorzellen sind Endothelzellen leichter zugänglich, da kein Tumorgewebe penetriert werden muß. Die Schädigung eines einzelnen Tumorgefäßes sollte zum Absterben tausender Tumorzellen führen. Um ein Tumorgefäß zu schädigen, besteht keine Notwendigkeit, alle Endothelzellen abzutöten. Der spezifische Angriff von Endothelzellen in oder in der Nähe von Tumoren minimiert systemische Nebenwirkungen. Endothelzellen sind genetisch sehr stabil, so dass die Wahrscheinlichkeit einer Resistenzentwicklung gegen das Tumortherapeutikum gering ist.

Im Rahmen der vorliegenden Erfindung wurde nun überraschenderweise eine Möglichkeit gefunden, die chemisch sehr empfindliche, hochfunktionalisierte Wirkstoffklasse der Epothilone und ihrer Analoga mit einer hochmolekularen Erkennungseinheit über unterschiedliche Linker an unterschiedliche Positionen des Wirkstoffes zu knüpfen.

Der vorliegenden Erfindung liegt somit unter anderem die Aufgabe zugrunde,

1. eine Methode zu finden, hoch aktive Wirkstoffe aus der Strukturklasse der Epothilone und Epothilon-Derivate mit geeigneten Linkern zu verknüpfen,
2. geeignete Linker zu synthetisieren,
3. eine Methode zu entwickeln, diese Epothilon-Linker Konjugate mit Erkennungseinheiten wie beispielsweise monoklonalen Antikörpern oder deren Fragmenten zu Immunkonjugaten zu verknüpfen, die sowohl chemisch als auch metabolisch für eine Arzneimittelentwicklung ausreichend stabil sind und die hinsichtlich ihrer therapeutischen Breite, ihrer Selektivität der Wirkung und/oder unerwünschter toxischer Nebenwirkungen und/oder ihrer Wirkstärke den zu Grunde liegenden Epothilonen bzw. Epothilon-Derivaten überlegen sind.

Die vorliegende Erfindung umfasst entsprechend Effektorkonjugate der allgemeinen Formel I



I,

worin

R^{1a}, R^{1b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_m$-Gruppe sind, worin m 2 bis 5 ist,

R^{2a}, R^{2b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_n$-Gruppe sind, worin n 2 bis 5 ist, oder C_2-C_{10} Alkenyl, oder C_2-C_{10} Alkinyl,

R^3 Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl, und

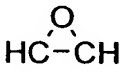
R^{4a}, R^{4b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_p$-Gruppe sind, worin p 2 bis 5 ist,

R^5 Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, CO_2H, CO_2Alkyl, CH_2OH, CH_2OAlkyl, CH_2OAcyl, CN, CH_2NH_2, CH_2N(Alkyl, Acyl)$_{1,2}$, oder CH_2Hal,

Hal ein Halogen-Atom,

R^6, R^7 jeweils Wasserstoff, oder gemeinsam eine zusätzliche Bindung, oder gemeinsam ein Sauerstoff-Atom, oder gemeinsam eine NH-Gruppe, oder gemeinsam eine N-Alkyl-Gruppe, oder gemeinsam eine CH_2-Gruppe, und

G ein Sauerstoffatom oder CH_2 sind,

D-E eine Gruppe H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, oder, falls G eine CH_2-Gruppe darstellt, CH_2-O ist,

W eine Gruppe C(=X)R^8, oder ein bi- or tricyclischer aromatischer oder heteroaromatischer Rest ist,

L^3 Wasserstoff ist, oder, falls ein Rest in W eine Hydroxyl-Gruppe enthält, mit dieser eine Gruppe O-L^4 bildet, oder, falls ein Rest in W eine Amino-Gruppe enthält, mit dieser eine Gruppe NR^{25}-L^4 bildet,

R^{25} Wasserstoff oder C_1-C_{10} Alkyl ist,

X ein Sauerstoffatom, oder zwei OR^{20}-Gruppen, oder eine C_2-C_{10} Alkylendioxy Gruppe, die geradkettig oder verzeigt sein darf, oder H/OR^9, oder eine $CR^{10}R^{11}$-Gruppe,

R^8 Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, Halogen oder CN, und

R^9 Wasserstoff oder eine Schutzgruppe PG^X sind,

R^{10}, R^{11} jeweils unabhängig voneinander Wasserstoff, C_1-C_{20} Alkyl, Aryl, Aralkyl sind, oder gemeinsam mit einem Methylenkohlenstoffatom einen 5- bis 7-gliedrigen carbocyclischen Ring bilden,

Z Sauerstoff oder H/OR^{12},

R^{12} Wasserstoff oder eine Schutzgruppe PG^Z,

A-Y eine Gruppe O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) oder NR^{21}-SO_2,

R^{20} C_1-C_{20} Alkyl,

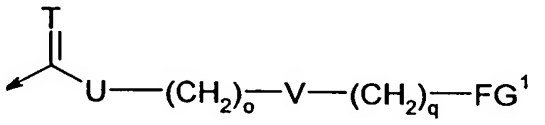
R^{21} ein Wasserstoffatom oder C_1-C_{10} Alkyl,

PG^X, PG^Y, PG^Z eine Schutzgruppe PG, und

L^1, L^2, L^4 unabhängig voneinander Wasserstoff, eine Gruppe C(=O)Cl, eine Gruppe C(=S)Cl, eine Gruppe PG^Y oder einen Linker der allgemeinen Formel (III) oder (IV) darstellen können;

mit der Bedingung, dass mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel (III) oder (IV) darstellt;

der Linker der allgemeinen Formel (III) folgende Struktur hat,



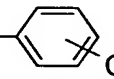
III,

worin

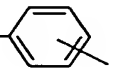
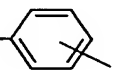
T Sauerstoff oder Schwefel,

U Sauerstoff, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)- oder NR^{24a},

o 0 bis 15,

V eine Bindung, Aryl, eine Gruppe NR^{24b}-C(=O)-O-$(CH_2)_s$-  -Q-, oder eine Gruppe NR^{24b}-C(=S)-O-$(CH_2)_s$-  -Q-,

s 0 bis 4,

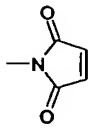
Q eine Bindung, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c}, -O-C(=O)-NR^{24c}-  , oder -O-C(=S)-NR^{24c}- 

R^{22} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl

R^{23} Wasserstoff oder C_1-C_{10} Alkyl,

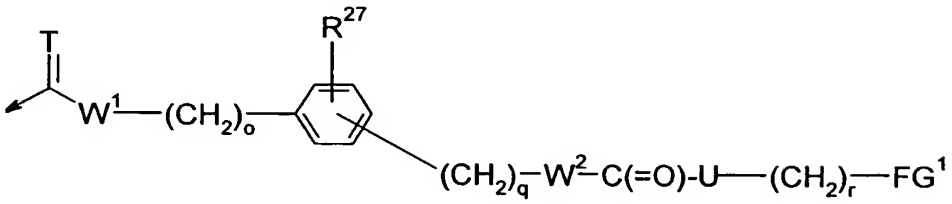
R^{24a}, R^{24b}, R^{24c} unabhängig voneinander Wasserstoff oder C_1-C_{10} Alkyl,

q 0 bis 15,

FG^1 C_1-C_{10} Alkyl-S_3 ,  , ,  ,  ,  ,  ,
oder CO_2H

darstellen können; und

der Linker der allgemeinen Formel (IV) folgende Struktur hat,



IV,

worin

T Sauerstoff oder Schwefel,

W^1, W^2 gleich oder verschieden sind und Sauerstoff oder NR^{24a},

o 0 bis 5,

R^{22} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl,

R^{23} Wasserstoff oder C_1-C_{10} Alkyl,

R^{24a} Wasserstoff oder C_1-C_{10} Alkyl,

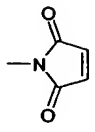
R^{27} Halogen, CN, NO_2, CO_2R^{28}, OR^{28},

R^{28} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl,

q 0 bis 5,

U Sauerstoff, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-, oder C_1-C_{20} Alkyl,

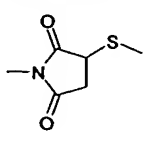
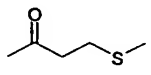
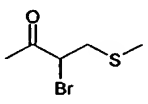
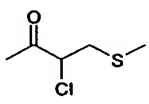
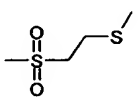
r 0 bis 20,

FG^1 C_1-C_{10} Alkyl-S_3,  ,  ,  ,  ,  oder CO_2H,

darstellen können;

als einheitliches Isomer oder eine Mischung unterschiedlicher Isomere und/oder als ein pharmazeutisch akzeptables Salz hiervon.

Die Erfindung beschreibt weiterhin die Herstellung von Effektor-Erkennungseinheit-Konjugaten der allgemeinen Formel (I), wobei die Substituenten darin die obengenannten Bedeutungen haben, jedoch mindestens eine Gruppe FG^1 durch eine Gruppe FG^{2a} oder FG^{2b} ersetzt ist, wobei FG^{2a} bzw. FG^{2b} die folgenden Bedeutungen haben können:

FG^{2a} -S-S-,  ,  ,  ,  , 

FG^{2b} -CONH-

und wobei eine Erkennungseinheit über ein Schwefelatom mit der Gruppe FG^{2a}, wobei das gezeigte Schwefelatom Bestandteil der Erkennungseinheit ist, oder über eine Amidfunktion der Gruppe FG^{2b}, wobei das gezeigte Stickstoffatom Bestandteil der Erkennungseinheit ist, konjugiert ist;
wobei die Erkennungseinheit beispielsweise ein Peptid, ein löslicher Rezeptor, ein Cytokin, ein Lymphokin, ein Aptamer, ein Spiegelmer, ein rekombinantes Protein, eine Framework-Struktur, ein monoklonaler Antikörper oder ein Fragment eines monoklonalen Antikörpers sein kann.

Gemäss dieser Erfindung können die genannten Effektor-Erkennungseinheit-Konjugate eine oder mehrere Erkennungseinheiten umfassen; dabei können die einem Konjugat zugehörigen Erkennungseinheiten identisch oder verschieden sein. Es ist bevorzugt, dass die Erkennungseinheiten eines Konjugats identisch sind.

Die erfindungsgemäßen Effektor-Erkennungseinheit-Konjugate können in Form ihrer α-, β- oder γ-Cyclodextrin-Clathrate oder in Form liposomaler oder pegylierter Zusammensetzungen verwendet werden.

Die erfindungsgemäßen Konjugate werden vorzugsweise für die Behandlung von Erkrankungen, die mit proliferativen Prozessen verknüpft sind, eingesetzt. Beispielsweise genannt seien die Therapie unterschiedlichster Tumore, die Therapie entzündlicher und/oder neurodegenerativer Erkrankungen wie der Multiplen Sklerose oder der Alzheimerschen Erkrankung, die Therapie Angiogenese-assoziierter Erkankungen wie das Wachstum solider Tumore, die rheumatoide Arthritis oder Erkrankungen des Augenhintergrundes.

Die Darstellung der Epothilone, ihrer Vorstufen und Derivate der allgemeinen Formel I erfolgt nach den dem Fachmann bekannten Methoden wie sie

beispielsweise in DE 19907588, WO 98/25929, WO 99/58534, WO 99/2514, WO 99/67252, WO 99/67253, WO 99/7692, EP 99/4915, WO 00/485, WO 00/1333, WO 00/66589, WO 00/49019, WO 00/49020, WO 00/49021, WO 00/71521, WO 00/37473, WO 00/57874,WO 01/92255, WO 01/81342, WO 01/73103, WO 01/64650, WO 01/70716, US 6204388, US 6387927, US 6380394, US 02/52028, US 02/58286, US 02/62030, WO 02/32844, WO 02/30356, WO 02/32844, WO 02/14323, WO 02/8440 beschrieben sind.

Als Alkylgruppen R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} und R^{26} sind gerad- oder verzweigtkettige Alkylgruppen mit 1-20 Kohlenstoffatomen zu betrachten, wie beispielsweise Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, tert.-Butyl, Pentyl, Isopentyl, Neopentyl, Heptyl, Hexyl, Decyl.

Die Alkylgruppen R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} und R^{26} können ferner perfluoriert oder substituiert sein durch 1-5 Halogenatome, Hydroxygruppen, C_1-C_4-Alkoxygruppen oder C_6-C_{12}-Arylgruppen (die durch 1-3 Halogenatome substituiert sein können).

Als Arylrest R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22}, R^{26} und V kommen substituierte und unsubstituierte carbocyclische oder heterocyclische Reste mit einem oder mehreren Heteroatomen wie Phenyl, Naphthyl, Furyl, Thienyl, Pyridyl, Pyrazolyl, Pyrimidinyl, Oxazolyl, Pyridazinyl, Pyrazinyl, Chinolyl, Thiazolyl, Benzothiazolyl oder Benzoxazolyl, die einfach oder mehrfach substituiert sein können durch Halogen, OH, O-Alkyl, CO_2H, CO_2-Alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl oder C_1-C_{20}-Acyloxy-Gruppen, in Frage. Die Heteroatome können oxidiert sein, sofern dadurch der aromatischen Charakter nicht verloren geht, wie beispielsweise die Oxidation eines Pyridyls zu einem Pyridyl-N-Oxid.

Als bi- und tricyclische Arylreste W kommen substituierte und unsubstituierte carbocyclische oder heterocyclische Reste mit einem oder mehreren Heteroatomen wie Naphthyl, Anthryl, Benzothiazolyl, Benzoxazolyl, Benzimidazolyl, Chinolyl, Isochinolyl, Benzoxazinyl, Benzofuranyl, Indolyl, Indazolyl, Chinoxalinyl, Tetrahydroisochinolinyl, Tetrahydrochinolinyl, Thienopyridinyl, Pyridopyridinyl, Benzopyrazolyl, Benzotriazolyl, oder Dihydroindolyl, die einfach oder mehrfach substituiert sein können durch Halogen, OH, O-Alkyl, CO_2H, CO_2-Alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl oder C_1-C_{20}-Acyloxy-Gruppen, in Frage. Die Heteroatome können oxidiert sein, sofern dadurch der aromatische Charakter nicht verloren geht, wie beispielsweise die Oxidation eines Chinolyls zu einem Chinolyl-N-Oxid.

Die Aralkylgruppen in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22} und R^{26} können im Ring bis 14 C-Atome, bevorzugt 6 bis 10 und in der Alkylkette 1 bis 8, bevorzugt 1 bis 4 Atome enthalten. Als Aralkylreste kommen beispielweise in Betracht Benzyl, Phenylethyl, Naphthylmethyl, Naphthylethyl, Furylmethyl, Thienylethyl oder Pyridylpropyl. Die Ringe können einfach oder mehrfach substituiert sein durch Halogen, OH, O-Alkyl, CO_2H, CO_2-Alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-Alkyl, C_1-C_{20}-Acyl oder C_1-C_{20}-Acyloxy-Gruppen.

Als Vertreter für die Schutzgruppen PG sind tris(C_1-C_{20} Alkyl)silyl, bis(C_1-C_{20} Alkyl)-Arylsilyl, (C_1-C_{20} Alkyl)-Diarylsilyl, tris(Aralkyl)-Silyl, C_1-C_{20}-Alkyl, C_2-C_{20}-Alkenyl, C_4-C_7-Cycloalkyl, das im Ring zusätzlich ein Sauerstoffatom enthalten kann, Aryl, C_7-C_{20}-Aralkyl, C_1-C_{20}-Acyl, Aroyl, C_1-C_{20}-Alkoxycarbonyl, C_1-C_{20}-Alkylsulfonyl sowie Arylsulfonyl zu nennen.

Als Alkyl-, Silyl- und Acylreste für die Schutzgruppen PG kommen insbesondere die dem Fachmann bekannten Reste in Betracht. Bevorzugt sind aus den entsprechenden Alkyl- und Silylethern leicht abspaltbare Alkyl- bzw. Silylreste, wie beispielsweise der Methoxymethyl-, Methoxyethyl, Ethoxyethyl-,

Tetrahydropyranyl-, Tetrahydrofuranyl-, Trimethylsilyl-, Triethylsilyl-, tert.-Butyldimethylsilyl-, tert.-Butyldiphenylsilyl-, Tribenzylsilyl-, Triisopropylsilyl-, Benzyl, para-Nitrobenzyl-, para-Methoxybenzyl-Rest sowie Alkylsulfonyl- und Arylsulfonylreste. Als Alkoxycarbonylrest kommt z.B. Trichlorethyloxycarbonyl (Troc) in Frage. Als Acylreste kommen z.B. Formyl, Acetyl, Propionyl, Isopropionyl, Trichlormethylcarbonyl, Pivalyl-, Butyryl oder Benzoyl, die mit Amino- und/oder Hydroxygruppen substituiert sein können, in Frage.

Als Aminoschutzgruppen PG kommen die dem Fachmann bekannten Reste in Betracht. Beispielsweise genannt seien die Alloc-, Boc-, Z-, Benzyl, f-Moc-, Troc-, Stabase- oder Benzostabase-Gruppe.

Als Halogen-Atome kommen in Betracht Fluor, Chlor, Brom oder Iod.

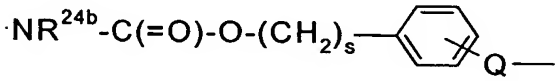
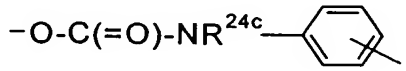
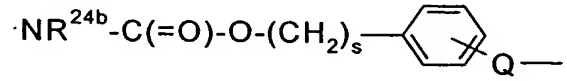
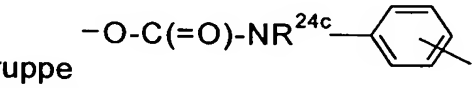
Die Acylgruppen können 1 bis 20 Kohlenstoffatome enthalten, wobei Formyl-, Acetyl-, Propionyl-, Isopropionyl und Pivalylgruppen bevorzugt sind.

Die für X mögliche C_2-C_{10}-Alkylen-α,ω-dioxygruppe ist vorzugsweise eine Ethylenketal- oder Neopentylketalgruppe.

Bevorzugte Verbindungen der allgemeinen Formel I sind solche, bei denen A-Y O-C(=O) oder NR^{21}-C(=O), D-E eine H_2C-CH_2-Gruppe, G eine CH_2-Gruppe, Z ein Sauerstoffatom, R^{1a}, R^{1b} jeweils C_1-C_{10} Alkyl oder zusammen eine $-(CH_2)_p$-Gruppe mit p gleich 2 oder 3 oder 4, R^{2a}, R^{2b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, C_2-C_{10} Alkenyl, oder C_2-C_{10} Alkinyl, R^3 Wasserstoff; R^{4a}, R^{4b} unabhängig voneinander Wasserstoff oder C_1-C_{10} Alkyl; R^5 Wasserstoff, oder C_1-C_4 Alkyl oder CH_2OH oder CH_2NH_2 oder $CH_2N(Alkyl, Acyl)_{1,2}$ oder CH_2Hal, R^6 und R^7 gemeinsam eine zusätzliche Bindung oder gemeinsam eine NH-Gruppe oder gemeinsam eine N-Alkyl-Gruppe oder

gemeinsam eine CH_2-Gruppe oder gemeinsam ein Sauerstoffatom, W eine Gruppe $C(=X)R^8$ oder ein 2-Methylbenzothiazol-5-yl-Radikal oder ein 2-Methylbenzoxazol-5-yl-Radikal oder ein Chinolin-7-yl-Radikal oder ein 2-Aminomethylbenzothiazol-5-yl-Radikal oder ein 2-Hydroxymethylbenzothiazol-5-yl-Radikal oder ein 2-Aminomethylbenzoxazol-5-yl-Radikal oder ein 2-Hydroxymethylbenzoxazol-5-yl-Radikal, X eine $CR^{10}R^{11}$-Gruppe, R^8 Wasserstoff oder C_1-C_4 Alkyl oder ein Fluoratom oder ein Chloratom oder ein Bromatom, R^{10}/R^{11} Wasserstoff/2-Methylthiazol-4-yl oder Wasserstoff/2-Pyridyl oder Wasserstoff/2-Methyloxazol-4-yl oder Wasserstoff/2-Aminomethylthiazol-4-yl oder Wasserstoff/2-Aminomethyloxazol-4-yl oder Wasserstoff/2-Hydroxymethylthiazol-4-yl oder Wasserstoff/2-Hydroxymethyloxazol-4-yl darstellen.

Als Linker der allgemeinen Formel (III) sind Verbindungen bevorzugt, bei denen V eine Bindung oder einen Arylrest darstellt, o gleich Null ist und T ein Sauerstoffatom darstellt.

Als Linker der allgemeinen Formel (III) sind weiterhin Verbindungen bevorzugt, bei denen V eine Bindung oder einen Arylrest oder eine Gruppe  darstellt; Q eine Bindung oder eine Gruppe  darstellt; und o 0 bis 4 ist. Besonders bevorzugt sind Verbindungen der allgemeinen Formel (III), wobei V eine Bindung oder eine Gruppe  darstellt; Q eine Bindung oder eine Gruppe  darstellt; o gleich 0, 2 oder 3 ist; s gleich 1 ist; und T ein Sauerstoffatom ist.

Als Linker der allgemeinen Formel (IV) sind Verbindungen bevorzugt, bei denen o null bis vier und q null bis drei ist. Besonders bevorzugt sind Verbindungen der allgemeinen Formel (IV), wobei o 0, 2 oder 3 ist; W^1 ein Sauerstoffatom ist; q gleich 0 ist; R^{22} Wasserstoff, C_1-C_3 Alkyl oder Aralkyl ist; R^{23} Wasserstoff oder C_1-C_3 Alkyl ist; R^{24a} Wasserstoff oder C_1-C_3 Alkyl ist; R^{27} Fluor, Chlor, CN, NO_2, CO_2R^{28} oder OR^{28} ist; R^{28} Wasserstoff oder C_1-C_5 Alkyl ist; und U Sauerstoff, CHR^{22} oder CHR^{22}-NR^{23}-C(=O)- ist.

Als rekombinante Proteine zur Verwendung als Erkennungseinheit kommen beispielsweise aus von Antikörpern abgeleitete Bindungsregionen, sogenannte CDRs in Frage.

Als Framework-Strukturen zur Verwendung als Erkennungseinheit kommen beispielsweise hochmolekulare Strukturen, die nicht von Antikörpern abgeleitet sind, in Frage. Beispielsweise genannt seien Strukturen vom Fibronektin-Typ 3 und von Crystallinen.

Als Fragmente monoklonaler Antikörper zur Verwendung als Erkennungseinheit seien beispielsweise genannt single-chain Fv, Fab, $F(ab)_2$ sowie rekombinante Multimere.

Als bevorzugte Erkennungseinheiten kommen solche in Betracht, die sich beispielweise für die Erkennung und/oder Diagnose und/oder Therapie von soliden Tumoren und malignen Erkrankungen des hämatopoetischen Systems eignen.

Als weiterhin bevorzugte Erkennungseinheiten kommen solche in Betracht, die eine selektive Erkennung des erkrankungsspezifischen Gefäßsystems, vorzugsweise der Angiogenese, ermöglichen.

Tabelle 1 führt Beispiele für besonders bevorzugte Erkennungseinheiten zur Behandlung solider Tumoren auf.

TABELLE 1

Tumor	Antigen Identität / Charakteristika	Monoklonale Antikörper	Referenzen
Gynekol. (GY)	CA 125' >200 kD mucin GP	OC 125	Kabawat et al., 1983; Szymendera, 1986
Ovarial	80 Kd GP	OC 133	Masuko et al., Cancer Res, 1984
Ovarial	'SGA' 360 Kd GP	OMI	de Krester et al., 1986
Ovarial	High M_r mucin	Mo v1	Miotti et al., Cancer Res, 1985
Ovarial	High M_r mucin/ glycolipid	Mo v2	Miotti et al., Cancer Res, 1985
Ovarial	NS	3C2	Tsuji et al., Cancer Res, 1985
Ovarial	NS	4C7	Tsuji et al., Cancer Res, 1985
Ovarial	High M_r mucin	ID3	Gangopadhyay et al., 1985
Ovarial	High M_r mucin	DU-PAN-2	Lan et al., 1985
GY	7700 Kd GP	F 36/22	Croghan et al., 1984
Ovarial	'gp 68' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
GY	40, 42kD GP	OV-TL3	Poels et al., 1986
GY	'TAG-72' High M_r mucin	B72.3	Thor et al., 1986
Ovarial	300-400 Kd GP	DF_3	Kufe et al., 1984

Ovarial	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985
GY	105 Kd GP	MF 116	Mattes et al., 1984
Ovarial	38-40 kD GP	Mov18	Miotti et al., 1987
GY	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Ovarial	CA 19-9 or GICA	CA 19-9 (1116NS 19-9)	Atkinson et al., 1982
Ovarial	'FLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Ovarial	72 Kd	791T/36	Perkins et al., 1985
Ovarial	69 Kd PLAP	$NDOG_2$	Sunderland et al., 1984
Ovarial	unbekannt M_r PLAP	H317	Johnson et al., 1981
Ovarial	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
Uterus, Ovar	HMFG-2	HMFG2	Epenetos et al., 1982
GY	HMFG-2	3.14.A3	Burchell et al., 1983
Brust	330-450 Kd GP	DF3	Hayes et al., 1985
Brust	NS	NCRC-11	Ellis et al., 1984
Brust	37kD	3C6F9	Mandeville et al., 1987
Brust	NS	MBE6	Teramoto et al., 1982
Brust	NS	CLNH5	Glassy et al., 1983
Brust	47 Kd GP	MAC 40/43	Kjeldsen et al., 1986
Brust	High M_r GP	EMA	Sloane et al., 1981
Brust	High M_r GP	HMFG1 HFMG2	Arklie et al., 1981
Brust	NS	3.15.C3	Arklie et al., 1981
Brust	NS	M3, M8, M24	Foster et al., 1982
Brust	1 (Ma) Blutgruppe Ags	M18	Foster et al., 1984

Brust	NS	67-D-11	Rasmussen et al., 1982
Brust	Estrogen Rezeptor	D547Sp, D75P3, H222	Kinsel et al., 1989
Brust	EGF Rezeptor	Anti EGF	Sainsbury et al., 1985
Brust	Laminin Rezeptor	LR-3	Horan Hand et al., 1985
Brust	*erb* B-2 p185	TA1	Gusterson et al., 1988
Brust	NS	H59	Hendler et al., 1981
Brust	126 Kd GP	10-3D-2	Soule et al., 1983
Brust	NS	HmAB1,2	Imam et al., 1984; Schlom et al., 1985
Brust	NS	MBR 1,2,3	Menard et al., 1983
Brust	95 Kd	24-17-1	Thompson et al., 1983
Brust	100 Kd	24-17-2 (3E1-2)	Croghan et al., 1983
Brust	NS	F36/22.M7/105	Croghan et al., 1984
Brust	24 Kd	C11, G3, H7	Adams et al., 1983
Brust	90 Kd GP	B6-2	Colcher et al., 1981
Brust	CEA & 180 Kd GP	B1-1	Colcher et al., 1983
Brust	Kolon & Pankreas mucin ähnlich Ca 19-9	Cam 17-1	Imperial Cancer Research Technology MAb listing
Brust	Milch mucin Kernprotein	SM3	Imperial Cancer Research Technology Mab listing
Brust	Milch mucin Kernprotein	SM4	Imperial Cancer Research Technology Mab listing

Brust	Affinitäts-gereinigtes Milch-mucin	C-Mul (566)	Imperial Cancer Research Technology Mab listing
Brust	$P185^{HER2}$	4D5 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, 5B8	Shepard et al., 1991
Brust	CA 125 >200 Kd GP	OC 125	Kabawat et al., 1985
Brust	High M_r mucin/ Glycolipid	MO v2	Miotti et al., 1985
Brust	High M_r mucin	DU-PAN-2	Lan et al., 1984
Brust	'gp48' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Brust	300-400 Kd GP	DF_3	Kufe et al., 1984
Brust	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986
Brust	'CEA' 180 Kd GP	ccccCEA 11	Wagener et al., 1984
Brust	'PLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Brust	HMFG-2 >400 Kd GP	3-14-A3	Burchell et al., 1983
Brust	NS	FO23C5	Riva et al., 1988
Kolorektal	TAG-72 High M_r mucin	B72-3	Colcher et al., 1987
Kolorektal	GP37	(17-1A) 1038-17-1A	Paul et al., 1986
Kolorektal	Surface GP	CO17-1A	LoBuglio et al., 1988
Kolorektal	CEA	ZCE-025	Patt et al., 1988
Kolorektal	CEA	AB2	Griffin et al., 1988a
Kolorektal	Zelloberflächen AG	HT-29-15	Cohn et al., 1987
Kolorektal	Sekretorisches Epithel	250-30.6	Leydem et al., 1986

Kolorektal	Oberflächen-Glycoprotein	44X14	Gallagher et al., 1986
Kolorektal	NS	A7	Takahashi et al., 1988
Kolorektal	NS	GA73-3	Munz et al., 1986
Kolorektal	NS	791T/36	Farrans et al., 1982
Kolorektal	Zellmebran & Zyto-plasmatisches Ag	28A32	Smith et al., 1987
Kolorektal	CEA & Vindesin	28.19.8	Corvalen, 1987
Kolorektal	gp72	X MMCO-791	Byers et al., 1987
Kolorektal	high M_r mucin	DU-PAN-2	Lan et al., 1985
Kolorektal	high M_r mucin	ID_3	Gangopadhyay et al., 1985
Kolorektal	CEA 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Kolorektal	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985
Kolorektal	CA-19-9 (or GICA)	CA-19-9 (1116NS 19-9)	Atkinson et al., 1982
Kolorektal	Lewis a	PR5C5	Imperial Cancer Research Technology Mab Listing
Kolorektal	Lewis a	PR4D2	Imperial Cancer Research Technology Mab Listing
Kolorektal	Kolon mucus	PR4D1	Imperial Cancer Research Technology Mab Listing
Melanom	p97a	4-1	Woodbury et al., 1980
Melanom	p97a	8-2 M_{17}	Brown, et al., 1981a
Melanom	p97b	96-5	Brown, et al., 1981a

Melanom	p97c	118-1, 133-2, (113-2)	Brown, et al., 1981a
Melanom	p97c	L_1, L_{10}, R_{10} (R_{19})	Brown et al., 1981b
Melanom	p97d	I_{12}	Brown et al., 1981b
Melanom	p97e	K_5	Brown et al., 1981b
Melanom	P155	6-1	Loop et al., 1981
Melanom	G_{D3} disialogan-glioside	R24	Dippold et al., 1980
Melanom	P210, p60, p250	5-1	Loop et al., 1981
Melanom	P280 p440	225.28S	Wilson et al., 1981
Melanom	GP 94, 75, 70 & 25	465.12S	Wilson et al., 1981
Melanom	P240-P250, P450	9-2-27	Reisfeld et al., 1982
Melanom	100, 77, 75 Kd	F11	Chee et al., 1982
Melanom	94 Kd	376.96S	Imai et al., 1982
Melanom	4 GP Ketten	465.12S	Imai et al., 1982; Wilson et al., 1981
Melanom	GP 74	15-75	Johnson & Reithmuller, 1982
Melanom	GP 49	15-95	Johnson & Reithmuller, 1982
Melanom	230 Kd	Mel-14	Carrel et al., 1982
Melanom	92 Kd	Mel-12	Carrel et al., 1982
Melanom	70 Kd	Me3-TB7	Carrel et al., 1:387, 1982
Melanom	HMW MAA ähnlich 9-2-27 AG	225.28SD	Kantor et al., 1982
Melanom	HMW MAA ähnlich 9-2-27 AG	763.24TS	Kantor et al., 1982

Melanom	GP95 ähnlich 376-96S 465-12S	705F6	Stuhlmiller et al., 1982
Melanom	GP125	436910	Saxton et al., 1982
Melanom	CD41	M148	Imperial Cancer Research Technology Mab listing
Gastro-intestinal (GI)	high M_r mucin	ID3	Gangopadhyay et al., 1985
Gallenblase, Pankreas, Magen	high M_r mucin	DU-PAN-2	Lan et al., 1985
Pankreas	NS	OV-TL3	Poels et al., 1984
Pankreas, Magen Ösophagus	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986
Magen	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Pankreas	HMFG-2 >400 Kd GP	3-14-A3	Burchell et al., 1983
GI	NS	C COLI	Lemkin et al., 1984
Pankreas, Magen	CA 19-9 (or GICA)	CA-19-9 (1116NS 19-9) und CA50	Szymendera, 1986
Pankreas	CA125 GP	OC125	Szymendera, 1986
Lunge nicht-klein-zelliges Lungen-karzinom (NSCLC)	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
NSCLC	high M_r mucin/ Glycolipid	MO v2	Miotti et al., 1985

NSCLC	'TAG -72' high M_r mucin	B72-3	Thor et al., 1986
NSCLC	High M_r mucin	DU-PAN-2	Lan et al., 1985
NSCLC	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984
Malignes Gliom	Zytoplastisches Antigen aus 85HG-22 Zellen	MUG 8-22	Stavrou, 1990
Malignes Gliom	Zelloberflächen Ag aus 85HG-\63 Zellen	MUC 2-63	Stavrou, 1990
Malignes Gliom	Zelloberflächen Ag aus 86HG-39 Zellen	MUC 2-39	Stavrou, 1990
Malignes Gliom	Zelloberfächen Ag aus 86HG-39 Zellen	MUG 7-39	Stavrou, 1990
GI, sonstige	P53	PAb 240, PAb 246, PAb 1801	Imperial Cancer Research Technology MaB Listing
Klein rundzellige Tumore	Neurale Zelladhäsions-Moleküle	ERIC-1	Imperial Cancer Research Technology MaB Listing
Medulloblastome, Neuroblastome, Rhabdomyosarcome		M148	Imperial Cancer Research Technology MaB Listing
Neuroblastome		FMH25	Imperial Cancer Research Technology MaB Listing
Nieren & Glioblastome	P155	6-1	Loop et al., 1981

Blasen & Laryngeal-Tumore	"Ca Antigen" 350-390 kD	CA1	Ashall et al., 1982
Neuroblastom	GD2	3F8	Cheung et al., 1986
Prostata	Gp48 48 kD GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Prostata	60 kD GP	$2C_8/2F_7$	Bhattacharya et al., 1985
Thyroid	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984

Als besonders bevorzugte Erkennungseinheiten zur Behandlung hämatologischer Tumore seien ferner Antikörper oder Antikörperfragmente wie CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21,CD5, CD37 und CD30 genannt.

Als besonders bevorzugte Erkennungseinheiten zur anti-angiogenen Therapie seien ferner Antikörper oder deren Fragmente wie VCAM, CD31, ELAM, Endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), Phosphatidylserin, PSMA, VEGFR/VEGF-Komplex oder ED-B-Fibronectin genannt.
Die nachstehend genannten Verbindungen sind als Effektor-Grundkörper erfindungsgemäß besonders bevorzugt:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion,
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion.

In einer erfindungsgemäßen Verbindung der allgemeinen Formel (I), enthaltend einen der obengenannten Grundkörper, sind die Wasserstoffatome in den obengenannten Grundkörpern an den in Formel (I) angegebenen Positionen durch Reste L^1-L^3 ersetzt, wobei die Reste L^1-L^3 die oben angegebenen Bedeutungen haben.

Die Erfindung betrifft ferner Linker der allgemeinen Formel III^1

$$RG^1—(CH_2)_o—V—(CH_2)_q—FG^1 \qquad III^1,$$

worin

RG^1 eine O=C=N-Gruppe oder eine S=C=N-Gruppe sein kann, und o, V, q und FG^1 die bereits oben genannten Bedeutungen haben,

sowie Linker der allgemeinen Formel III^2

$$RG^2—(CH_2)_o—V—(CH_2)_q—FG^1 \qquad III^2,$$

worin

RG^2 eine Hal-C(=T)-CHR^{22}-Gruppe oder eine Hal-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe sein kann, R^{26} C_1-C_{10} Alkyl, Aryl, Aralkyl sein kann, und o, V, q, T und FG^1 die bereits oben genannten Bedeutungen haben,

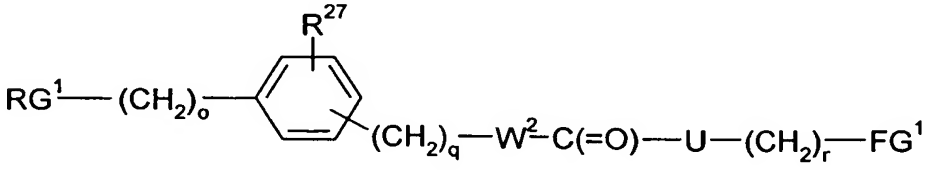
sowie Linker der allgemeinen Formel III^3

$$RG^3—(CH_2)_o—V—(CH_2)_q—FG^1 \qquad III^3,$$

worin

RG^3 eine OH-Gruppe oder eine NHR^{24a}-Gruppe oder eine COOH-Gruppe sein kann, und o, V, q und FG^1 die bereits oben genannten Bedeutungen haben;
jedoch mit der Bedingung, dass die Verbindung 1-(4-Amino-phenyl)-pyrrol-2,5-dion nicht umfasst ist.

Die Erfindung betrifft ferner Linker der allgemeinen Formel (IV^1):

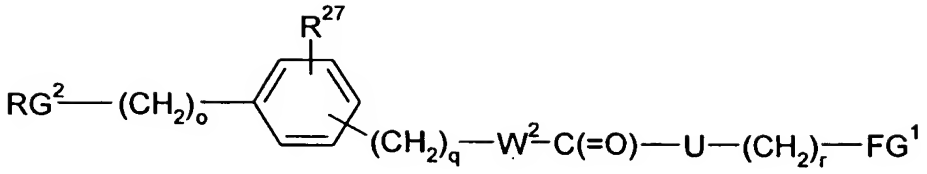


IV^1

worin

RG^1 eine O=C=N-Gruppe oder eine S=C=N-Gruppe ist, und o, q, r, W^2, R^{27}, U und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (IV^2):

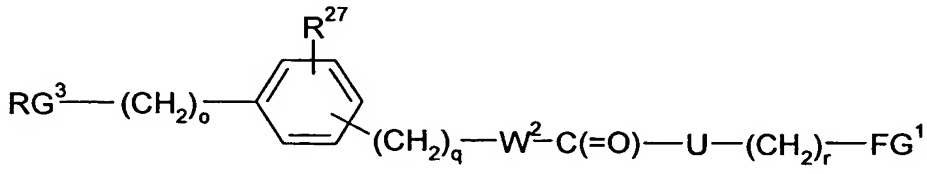


IV²

worin

RG² eine Hal-C(=T)-CHR²²-Gruppe oder eine Hal-C(=T)-CHR²²-NR²³-C(=T)-Gruppe oder eine R²⁶-C(=O)-O-C(=T)-CHR²²-Gruppe oder eine R²⁶-C(=O)-O-C(=T)-CHR²²-NR²³-C(=T)-Gruppe ist, wobei R²⁶ C_1-C_{10} Alkyl, Aryl, Aralkyl ist, und R²², R²³, T, o, q, r, W², R²⁷, U und FG¹ die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (IV³):



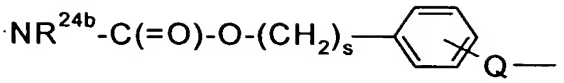
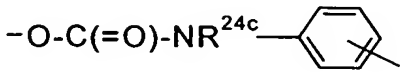
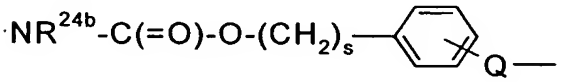
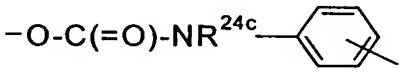
IV³

worin

RG³ eine OH-Gruppe oder eine NHR^24a-Gruppe oder eine COOH-Gruppe ist, und R^24a, o, q, r, W², R²⁷, U und FG¹ die in Anspruch 1 genannten Bedeutungen haben.

Erfindungsgemäss bevorzugt sind Linker der allgemeinen Formeln III¹, III² oder III³, wobei V eine Bindung oder einen Arylrest darstellt, o gleich Null ist und T ein Sauerstoffatom ist.

Weiterhin sind erfindungsgemäß Linker der allgemeinen Formeln III¹, III² oder III³ bevorzugt, bei denen V eine Bindung oder einen Arylrest oder eine Gruppe


darstellt; Q eine Bindung oder eine Gruppe  darstellt; und o 0 bis 4 ist. Besonders bevorzugt sind hieraus solche Linker, bei denen V eine Bindung oder eine Gruppe 
darstellt; Q eine Bindung oder eine Gruppe  darstellt; o gleich 0, 2 oder 3 ist; s gleich 1 ist; und T ein Sauerstoffatom ist.

Erfindungsgemäss bevorzugt sind weiterhin Linker der allgemeinen Formeln IV^1, IV^2 oder IV^3, bei denen o null bis vier und q null bis drei ist. Besonders bevorzugt sind hieraus solche Linker, bei denen o 0, 2 oder 3 ist; W^1 ein Sauerstoffatom ist; q gleich 0 ist; R^{22} Wasserstoff, C_1-C_3 Alkyl oder Aralkyl ist; R^{23} Wasserstoff oder C_1-C_3 Alkyl ist; R^{24a} Wasserstoff oder C_1-C_3 Alkyl ist; R^{27} Fluor, Chlor, CN, NO_2, CO_2R^{28} oder OR^{28} ist; R^{28} Wasserstoff oder C_1-C_5 Alkyl ist; und U Sauerstoff, CHR^{22} oder CHR^{22}-NR^{23}-C(=O)- ist.

Die Erfindung betrifft ferner Verfahren,

einen Linker der allgemeinen Formel III^1 oder IV^1

mit einer Verbindung der allgemeinen Formel I, worin die Bedingung, dass mindestens eine Gruppe L^1, L^2 oder L^4 einen Linker darstellt, nicht erfüllt sein muss, und worin L^1 und/oder L^2 und/oder L^4 die Bedeutung eines Wasserstoffatomes haben und freie, für die Umsetzung nicht benötigte Hydroxyl- und/oder Amino-Gruppen gegebenenfalls geschützt sind, umzusetzen,

einen Linker der allgemeinen Formel III^2 oder IV^2
mit einer Verbindung der allgemeinen Formel I, worin die Bedingung, dass mindestens eine Gruppe L^1, L^2 oder L^4 einen Linker darstellt, nicht erfüllt sein muss, und L^1 und/oder L^2 und/oder L^4 die Bedeutung eines Wasserstoffatomes haben und freie, für die Umsetzung nicht benötigte Hydroxyl- und/oder Amino-Gruppen gegebenenfalls geschützt sind, umzusetzen, oder

einen Linker der allgemeinen Formel III^3 oder IV^3
mit einer Verbindung der allgemeinen Formel I, worin die Bedingung, dass mindestens eine Gruppe L^1, L^2 oder L^4 einen Linker darstellt, nicht erfüllt sein muss, und L^1 und/oder L^2 und/oder L^4 die Bedeutung einer C(=O)Hal-Gruppe oder einer C(=S)Hal-Gruppe haben und freie, für die Umsetzung nicht benötigte Hydroxyl- und/oder Amino-Gruppen gegebenenfalls geschützt sind, umzusetzen.

Die Erfindung betrifft ferner die Verwendung einer Verbindung der allgemeinen Formel I, wobei die Substituenten die oben genannten Bedeutungen haben, jedoch die Bedingung, dass mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel III oder IV darstellt, nicht erfüllt sein muss, und mindestens ein Substituent L^1, L^2 oder L^4 Wasserstoff, eine Gruppe C(=O)Cl, oder eine Gruppe C(S)Cl darstellt, in einem Verfahren wie oben beschrieben.

Die Erfindung betrifft ferner die Verwendung einer Verbindung der allgemeinen Formel I, wobei die Substituenten die oben genannten Bedeutungen haben, jedoch die Bedingung, dass mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel III oder IV darstellt, nicht erfüllt sein muss, und mindestens ein Substituent L^1, L^2 oder L^4 Wasserstoff, eine Gruppe C(=O)Cl, oder eine Gruppe C(S)Cl darstellt, zur Herstellung eines Effektor-Erkennungseinheit-Konjugats wie oben beschrieben.

Die Erfindung betrifft ferner die Verwendung eines Linkers der allgemeinen Formel III^1, III^2, III^3, IV^1, IV^2 oder IV^3 zur Herstellung eines Effektor-Konjugats, wie oben beschrieben.

Die Erfindung betrifft ferner die Verwendung eines Linkers der allgemeinen Formel III^1, III^2, III^3, IV^1, IV^2 oder IV^3 zur Herstellung eines Effektor-Erkennungseinheit-Konjugats wie oben beschrieben.

Die Erfindung betrifft ferner die Verwendung einer Erkennungseinheit, wie vorstehend beschrieben, in einem der erfindungsgemäßen Verfahren zur Herstellung eines Effektor-Erkennungseinheit-Konjugats, wie oben beschrieben.

Die Erfindung betrifft ferner die erfindungsgemäßen Effektor-Erkennungseinheit-Konjugate zur Verwendung als Medikament oder zur Herstellung eines Medikaments oder einer pharmazeutischen Zusammensetzung.

Die Erfindung betrifft schließlich die Verwendung der erfindungsgemäßen Effektor-Erkennungseinheit-Konjugate zur Herstellung von Medikamenten für die Behandlung von Erkrankungen, die mit proliferativen Prozessen verknüpft sind, wie Tumore, entzündliche und/oder neurodegenerative Erkrankungen, Multiple Sklerose, Morbus Alzheimer, oder für die Behandlung von Angiogenese-assoziierten Erkrankungen, wie Tumorwachstum, rheumatoide Arthritis oder Erkrankungen des Augenhintergrundes.

Beispiele zur Synthese von Linkern (L)

Beispiel L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propansäure

Beispiel L1a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-propansäure ethylester

Die Lösung von 15g (89,5 mmol) N-Methylalaninethylester-Hydrochlorid in 850 ml wasserfreiem Tetrahydrofuran versetzt man bei 23°C mit 4,1 g einer ca. 60%igen Natriumhydrid-Dispersion und nach 3 Stunden mit 23,5 g 3-Acetylsulfanyl-propansäurechlorid. Man lässt 2 Tage reagieren, versetzt mit gesättigter Natriumhydrogencarbonatlösung und extrahiert mehrfach mit Ethylacetat. Die vereinigten organischen Extrakte wäscht man mit gesättigter Natriumchloridlösung, trocknet über Natriumsulfat und reinigt den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand durch Chromatographie an feinem Kieselgel. Isoliert werden 17,6 g (67,3 mmol, 75%) der Titelverbindung als farbloses Öl.

Beispiel L1b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propansäure

Die Lösung von 17,6 g (67,3 mmol) der nach Beispiel L1a dargestellten Verbindung in 150 ml Methanol versetzt man bei 23°C mit 44 ml einer 5M Natronlauge und rührt 5 Stunden. Durch Zugabe einer 4N Salzsäure stellt man einen pH von 2 ein und extrahiert mit Dichlormethan. Die vereinigten organischen Extrakte wäscht man mit gesättigter Natriumchloridlösung und trocknet über Natriumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand (13,0 g, max. 67,3 mmol) setzt man ohne Reinigung weiter um.

Beispiel L1c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propansäure methylester

Die Lösung von 4,53 g (max. 23,7 mmol) des nach Beispiel L1b dargestellten Rohproduktes in 135 ml Diethylether verestert man bei 0°C mit einer etherischen

Lösung von Diazomethan. Nach Lösungsmittelabzug isoliert man 4,59 g (22,4 mmol, 94%) der Titelverbindung als blass gelbes Öl, das man ohne Reinigung weiter umsetzt.

Beispiel L1d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propansäure methylester

Zu der Lösung von 21 g 2-Methyldisulfanyl-isoindol-1,3-dion in 420 ml Trichlormethan gibt man die Lösung von 14 g (68,2 mmol) der nach Beispiel L1c dargestellten Verbindung in 180 ml Trichlormethan und rührt 16 Stunden bei 23°C. Man engt ein, nimmt in Dichlormethan auf und rührt 0,5 Stunden. Feststoff wird abfiltriert, das Filtrat eingeengt und der Rückstand durch Chromatographie an feinem Kieselgel gereinigt. Isoliert werden 16,2 g (57,2 mmol, 84%) der Titelverbindung als farbloses Öl.

Beispiel L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propansäure

Die Lösung von 10 g (35,3 mmol) der nach Beispiel L1d dargestellten Verbindung in 20 ml Ethanol versetzt man mit 1l pH7 Phosphatpuffer, Schweineleberesterase und inkubiert bei 27°C 46 Stunden. Durch Zugabe einer 4N Salzsäure stellt man auf pH1 ein, extrahiert mit Dichlormethan, trocknet über Natriumsulfat und isoliert nach Filtration und Lösungsmittelabzug 8,3 g (30,8 mmol, 87%) der Titelverbindungn als farbloses Öl, das ohne weitere Reinigung umgesetzt wird.

^{1}H-NMR ($CDCl_3$): δ = 1,43+1,51 (3H), 2,55+2,63 (3H), 2,87 (2H), 2,88+3,00 (3H), 3,08-3,26 (2H), 4,63+5,19 (1H), 7,90 (1H) ppm.

Beispiel L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-essigsäure

Beispiel L2a

2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-essigsäure ethylester

7,13 g (46,4 mmol) N-Methylglycinethylester-Hydrochlorid setzt man in Analogie zu Beispiel L1a um und isoliert 6,9 g (27,9 mmol, 60%) der Titelverbindung als farbloses Öl.

Beispiel L2b

[(3-Mercapto-propionyl)-methyl-amino]-essigsäure

7,6 g (30,7 mmol) der nach Beispiel L2a dargestellten Verbindung setzt man in Analogie zu Beispiel L1b um und isoliert 4,92 g (27,8 mmol, 90%) der Titelverbindung als farbloses Öl.

Beispiel L2c

[(3-Mercapto-propionyl)-methyl-amino]-essigsäure methylester

4,92 g (27,8 mmol) der nach Beispiel L2b dargestellten Verbindung setzt man in Analogie zu Beispiel L1c um und isoliert 5,01 g (26,2 mmol, 94%) der Titelverbindung als farbloses Öl.

Beispiel L2d

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-essigsäure methylester

2,00 g (10,5 mmol) der nach Beispiel L2c dargestellten Verbindung setzt man in Analogie zu Beispiel L1d um und isoliert 2,33 g (8,65 mmol, 82%) der Titelverbindung als farbloses Öl.

Beispiel L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-essigsäure

2,00 g (7,83 mmol) der nach Beispiel L2d dargestellten Verbindung setzt man in Analogie zu Beispiel L1 um und isoliert 0,64 g (2,51 mmol, 32%) der Titelverbindung als farbloses Öl.

^{1}H-NMR ($CDCl_3$): δ = 2,41+2,56 (3H), 2,61-3,27 (7H), 3,98 (2H), 4,38 (1H) ppm.

Beispiel L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propionsäure

Beispiel L3a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-3-phenyl-propansäure ethylester

7,73 g (31,7 mmol) N-Methylphenylalaninethylester-Hydrochlorid setzt man in Analogie zu Beispiel L1a um und isoliert 2,3 g (6,82 mmol, 22%) der Titelverbindung als farbloses Öl.

Beispiel L3b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propansäure

1,09 g (3,23 mmol) der nach Beispiel L3a dargestellten Verbindung setzt man in Analogie zu Beispiel L1b um und isoliert 0,744 g (2,78 mmol, 86%) der Titelverbindung als farbloses Öl.

Beispiel L3c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propansäure methylester

0,74 g (2,77 mmol) der nach Beispiel L3b dargestellten Verbindung setzt man in Analogie zu Beispiel L1c um und isoliert 0,77 g (2,74 mmol, 99%) der Titelverbindung als farbloses Öl.

Beispiel L3d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propansäure methylester

0,77 g (2,74 mmol) der nach Beispiel L3c dargestellten Verbindung setzt man in Analogie zu Beispiel L1d um und isoliert 0,72 g (2,00 mmol, 73%) der Titelverbindung als farbloses Öl.

Beispiel L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propansäure

0,72 g (2,00 mmol) der nach Beispiel L3d dargestellten Verbindung setzt man in Analogie zu Beispiel L1 um und isoliert 0,49 g (1,42 mmol, 71%) der Titelverbindung als farbloses Öl.

Beispiel L4

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure

20,0 g (193,9 mmol) 4-Aminobuttersäure versetzt man mit 19 g Maleinsäureanhydrid, 290 ml Essigsäure und erhitzt 4 Stunden im 130°C heissen Ölbad. Man engt unter wiederholtem Zusatz von Toluol azeotrop ein, nimmt den Rückstand in Dichlormethan auf und reinigt durch Chromatographie an feinem Kieselgel. Isoliert werden 17,1 g (93,4 mmol, 48%) der Titelverbindung als kristallinen Feststoff.

^{1}H-NMR ($CDCl_3$): δ = 1,93 (2H), 2,38 (2H), 3,60 (2H), 6,71 (2H) ppm.

Beispiel L4a

1-(3-Isocyanato-propyl)-pyrrol-2,5-dion

5,0 g (27,3 mmol) der nach Beispiel L4 dargestellten Verbindung löst man in 90 ml Tetrahydrofuran, versetzt mit 8 ml Triethylamin, 6,17 ml Phosphorsäurediphenylesterazid und rührt 1,5 Stunden bei 23°C. Anschließend versetzt man mit 110 ml Toluol, destilliert das Tetrahydrofuran ab und erwärmt 2 Stunden auf 70°C. Das Rohprodukt reinigt man durch Chromatographie an feinem Kieselgel. Isoliert werden 1,77 g (9,82 mmol, 36%) der Titelverbindung.

Beispiel L5

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure

100 g (762 mmol) 6-Aminocapronsäure setzt man in Analogie zu Beispiel L5 um und isoliert 93,8 g (444 mmol, 58%) der Titelverbindung als kristallinen Feststoff.

^{1}H-NMR ($CDCl_3$): δ = 1,34 (2H), 1,55-1,70 (4H), 2,34 (2H), 3,51 (2H), 6,69 (2H) ppm.

Beispiel L5a

1-(5-Isocyanato-pentyl)-pyrrol-2,5-dion

10,0 g (47,3 mmol) der nach Beispiel L5 dargestellten Verbindung setzt man in Analogie zu Beispiel L4a um und isoliert 3,19 g (15,3 mmol, 32%) der Titelverbindung als farbloses Öl.

Beispiel L6

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure

10 g (49,7 mmol) 11-Aminoundecansäure setzt man in Analogie zu Beispiel L5 um und isoliert 6,29 g (22,4 mmol, 45%) der Titelverbindung als kristallinen Feststoff.

^{1}H-NMR ($CDCl_3$): δ = 1,19-1,36 (12H), 1,51-1,67 (4H), 2,34 (2H), 3,49 (2H), 6,68 (2H) ppm.

Beispiel L6a

1-(10-Isocyanato-decyl)-pyrrol-2,5-dion

5,28 g (18,8 mmol) der nach Beispiel L6 dargestellten Verbindung setzt man in Analogie zu Beispiel L4a um und isoliert 3,37 g (12,1 mmol, 64%) der Titelverbindung als farbloses Öl.

Beispiel L7

1-(4-Amino-phenyl)-pyrrol-2,5-dion

Die Lösung von 21,6 g (200 mmol) 1,4-Phenylendiamin in 200 ml Tetrahydrofuran versetzt man über 1,5 Stunden mit der Lösung von 19,6 g Maleinsäureanhydrid und rührt 22 Stunden bei 23°C. Man filtriert, wäscht mit Tetrahydrofuran nach und trocknet das Filtrat. Isoliert werden 37,1 g (197 mmol, 98%) der Titelverbindung als kristalliner Feststoff.

^{1}H-NMR (d6-DMSO): δ = 6,28 (1H), 6,48 (1H), 6,53 (2H), 7,30 (2H), 7,50-9,00 (2H) ppm.

Beispiel L8

1-(4-Hydroxy-phenyl)-pyrrol-2,5-dion

Die Suspension aus 5,0 g (45,8 mmol) 4-Aminophenol, 4,49 g Maleinsäureanhydrid und 40 ml Essigsäure erhitzt man 3 Stunden unter Rückfluss.

Man engt ein, enfernt restliche Essigsäure azeotrop durch wiederholte Destillation mit Essigsäure und reinigt den Rückstand durch Chromatographie an feinem Kieselgel. Isoliert werden 2,83 g (15,0 mmol, 33%) der Titelverbindung.

^{1}H-NMR (d6-DMSO): δ = 6,83 (2H), 7,09 (2H), 7,13 (2H), 9,71 (1H) ppm.

Beispiel L9

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-hydroxymethyl-2-nitro-phenyl ester

Die Lösung von 5,0 g (29,6 mmol) 4-Hydroxymethyl-2-nitro-phenol in 250 ml Dichlormethan versetzt man mit 6,1 g N,N'-Dicyclohexylcarbodiimid, 2,4 ml Pyridin und tropft innerhalb von 15 Minuten die Lösung von 5,5 g der nach Beispiel L4 dargestellten Verbindung in 250 ml Dichlormethan zu. Man rührt noch 1 Stunde bei 23°C, filtriert, engt das Filtrat ein und reinigt durch Chromatographie an feinem Kieselgel. Isoliert werden 1,73 g (5,2 mmol, 18%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 2,07 (3H), 2,67 (2H), 3,67 (2H), 4,79 (2H), 6,72 (2H), 7,28 (1H), 7,66 (1H), 8,10 (1H) ppm.

Beispiel L10

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-hydroxymethyl-2-nitro-phenyl ester

In Analogie zu Beispiel L9 setzt man 5,0 g (29,6 mmol) 4-Hydroxymethyl-2-nitro-phenol mit 6,34 g der nach Beispiel L5 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 3,78 g (10,4 mmol, 35%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,42 (2H), 1,66 (2H), 1,88 (2H), 2,64 (2H), 3,55 (2H), 4,78 (2H), 6,69 (2H), 7,21 (1H), 7,64 (1H), 8,09 (1H) ppm.

Beispiel L11

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-hydroxymethyl-2-nitro-phenyl ester

In Analogie zu Beispiel L9 setzt man 5,0 g (29,6 mmol) 4-Hydroxymethyl-2-nitrophenol mit 8,44 g der nach Beispiel L6 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 3,78 g (10,4 mmol, 35%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,21-1,63 (14H), 1,76 (2H), 1,99 (1H), 2,63 (2H), 3,51 (2H), 4,78 (2H), 6,68 (2H), 7,21 (1H), 7,65 (1H), 8,10 (1H) ppm.

Beispiele zur Synthese von Effektor-Linker-Konjugaten (EL)

Beispiel EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Beispiel EL1a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion

Die Lösung von 6,0g (7,93 mmol) (4S,7R,8S,9S,13Z,16S)-7-Allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion, das man in Analogie zu dem in WO 00/66589 beschrieben Verfahren hergestellt hat, in 186 ml wasserfreiem Dichlormethan versetzt man bei 0°C mit 26,4 ml einer 20%igen Lösung von Trifluoressigsäure in Dichlormethan und rührt 6 Stunden bei 0°C. Man gießt in gesättigte Natriumhydrogencarbonatlösung, extrahiert mit Dichlormethan, wäscht die vereinigten organischen Extrakte mit Wasser und trocknet über Magnesiumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an feinem Kieselgel. Isoliert werden 3,32 g (5,17 mmol, 65%) der Titelverbindung als farbloser Feststoff.

^{1}H-NMR ($CDCl_3$): δ = 0,09 (3H), 0,12 (3H), 0,93 (9H), 1,00 (3H), 1,06 (3H), 1,22 (3H), 1,70 (3H), 1,03-1,77 (5H), 1,95 (1H), 2,31-2,56 (6H), 2,83 (3H), 2,87 (1H), 3,00 (1H), 3,30 (1H), 3,90 (1H), 4,09 (1H), 4,94-5,03 (2H), 5,20 (1H), 5,77 (1H), 5,88 (1H), 7,34 (1H), 7,78 (1H), 7,95 (1H) ppm.

Beispiel EL1b

(4S,7R,8S,9S,13Z,16S)-3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) der nach Beispiel EL1a dargestellten Verbindung löst man in einem Gemisch aus 1,5 ml Trichlormethan und 1,5 ml Dimethylformamid, versetzt mit 144 mg des nach Beispiel L4a dargestellten Linkers, 79 mg Kupfer-(I)-chlorid und erhitzt 18 Stunden auf 70°C. Das Rohgemisch reinigt man durch Chromatographie an Dünnschichtplatten und isoliert 51 mg (62 µmol, 80%) der Titelverbindung als farbloses Öl.

Beispiel EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Die Lösung von 41 mg (50 µmol) der nach Bespiel 1b dargestellten Verbindung in einem Gemisch aus 0,8 ml Tetrahydrofuran und 0,8 ml Acetonitril versetzt man 310 µl Hexafluorkieselsäure, 310 µl Fluorwasserstoff-Pyridin-Komplex und rührt 23 Stunden bei 23°C. Man gießt in eine 5%ige Natronlauge, extrahiert mit Ethylacetat, wäscht die vereinigten organischen Extrakte mit einer gesättigten Natriumchloridlösung und trocknet über Natriumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an Dünnschichtplatten und isoliert 26 mg (36,7 µmol, 73%) der Titelverbindung als farblosen Schaum.

^{1}H-NMR ($CDCl_3$): δ = 0,99 (3H), 1,14 (3H), 1,17 (3H), 1,20-1,51 (3H), 1,54-1,87 (6H), 1,70 (3H), 2,22 (1H), 2,28-3,02 (9H), 2,83 (3H), 3,31 (1H), 3,45 (1H), 3,68 (1H), 4,44+4,83 (1H), 4,99 (1H), 5,03 (1H), 5,15 (1H), 5,61 (1H), 5,72 (1H), 5,91 (1H), 6,68 (2H), 7,36 (1H), 7,78 (1H), 7,90 (1H) ppm.

Beispiel EL2

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) und (1R,3S,7S,10R,11S,12S,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-

carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

Die Lösung von 44 mg (62,2 µmol) der nach Bespiel 1 dargestellten Verbindung in 2,0 ml Dichlormethan kühlt man auf -50°C und versetzt portionsweise über einen Zeitraum von 1,5 Stunden mit insgesamt 1,7 ml einer ca. 0,1 M Lösung von Dimethyldioxiran in Aceton. Man gießt in eine gesättigte Natriumthiosulfatlösung, extrahiert mit Dichlormethan und trocknet die vereinigten organischen Extrakte über Natriumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an Dünnschichtplatten und isoliert 22,7 mg (31,4 µmol, 50%) der Titelverbindung A sowie 7,6 mg (10,5 µmol, 17%) der Titelverbindung B jeweils als farblosen Schaum.

^{1}H-NMR ($CDCl_3$) von A: δ = 1,01 (3H), 1,14 (3H), 1,16 (3H), 1,20-1,94 (8H), 1,32 (3H), 2,11-2,74 (9H), 2,82 (1H), 2,84 (3H), 3,30 (2H), 3,48 (2H), 3,68 (1H), 4,36+4,93 (1H), 4,99 (1H), 5,04 (1H), 5,54 (1H), 5,69 (1H), 6,05 (1H), 6,68 (2H), 7,32 (1H), 7,80 (1H), 7,88 (1H) ppm.

^{1}H-NMR ($CDCl_3$) von B: δ = 1,02 (6H), 1,26 (3H), 1,33 (1H), 1,23-2,27 (12H), 2,54-2,78 (4H), 2,82 (3H), 2,91 (1H), 3,13 (1H), 3,40 (2H), 3,66 (1H), 4,11 (1H), 4,84 (1H), 4,95 (1H), 5,01 (1H), 5,70 (1H), 5,81+5,93 (1H), 6,04+6,13 (1H), 6,69 (2H), 7,35 (1H), 7,75 (1H), 7,90+7,99 (1H) ppm.

Beispiel EL3

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Beispiel EL3a

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) der nach Beispiel EL1a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1b mit dem nach Beispiel L5a hergestellten Linker um und

isoliert nach Reinigung 39 mg (45,9 µmol, 59%) der Titelverbindung als farbloses Öl.

Beispiel EL3

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

84 mg (98,8 µmol) der nach Beispiel EL3a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1 um und isoliert nach Reinigung 43 mg (58,4 µmol, 59%) der Titelverbindung als farblosen Schaum.

^{1}H-NMR ($CDCl_3$): δ = 0,89 (3H), 0,96 (3H), 0,85-1,97 (17H), 1,12 (3H), 2,16-3,01 (10H), 2,82 (3H), 3,44 (1H), 3,65 (1H), 4,41+4,53 (1H), 4,98 (1H), 5,03 (1H), 5,15 (1H), 5,60 (1H), 5,71 (1H), 5,90 (1H), 6,68 (2H), 7,35 (1H), 7,77 (1H), 7,89+7,96 (1H) ppm.

Beispiel EL4

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) und 1R,3S,7S,10R,11S,12S,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

26 mg (35,3 µmol) der nach Beispiel EL3 dargestellten Verbindung setzt man in Analogie zu Beispiel EL2 um und isoliert nach Reinigung 9,1 mg (12,1 µmol, 34%) der Titelverbindung A sowie 3,0 mg (4,0 µmol, 11%) der Titelverbindung B jeweils als farblosen Schaum.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,83-1,94 (15H), 0,98 (3H), 1,14 (3H), 1,16 (3H), 1,32 (3H), 2,15-2,82 (8H), 2,84 (3H), 3,44 (2H), 3,51 (1H), 3,66 (1H), 4,46 (1H), 4,99 (1H), 5,04 (1H), 5,54 (1H), 5,69 (1H), 6,06 (1H), 6,68 (2H), 7,33 (1H), 7,80 (1H), 7,89 (1H) ppm.

^{1}H-NMR ($CDCl_3$) von B: δ = 0,78-2,74 (23H), 1,01 (3H), 1,03 (3H), 1,33 (3H), 2,82 (3H), 2,91 (1H), 3,14 (1H), 3,39 (1H), 3,47 (2H), 3,67 (1H), 4,12 (1H), 4,49 (1H), 4,92-5,06 (2H), 5,53+5,80 (1H), 5,69 (1H), 6,11 (1H), 6,68 (2H), 7,34 (1H), 7,74+7,79 (1H), 7,89+8,02 (1H) ppm.

Beispiel EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Beispiel EL5a

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbaminsäure-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) der nach Beispiel EL1a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1b mit dem nach Beispiel L6a hergestellten Linker um und isoliert nach Reinigung 56 mg (60,8 µmol, 78%) der Titelverbindung als farbloses Öl.

Beispiel EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbaminsäure-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

20 mg (21,7 µmol) der nach Beispiel EL5a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1 um und isoliert nach Reinigung 10 mg (12,4 µmol, 57%) der Titelverbindung als farblosen Schaum.

^{1}H-NMR ($CDCl_3$): δ = 0,91-1,87 (22H), 0,97 (3H), 1,13 (3H), 1,17 (3H), 1,70 (3H), 2,18-2,69 (8H), 2,80 (1H), 2,82 (3H), 2,96 (1H), 3,47 (1H), 3,50 (2H), 3,66 (1H), 3,97+4,36 (1H), 4,98 (1H), 5,04 (1H), 5,16 (1H), 5,61 (1H), 5,72 (1H), 5,91 (1H), 6,68 (2H), 7,37 (1H), 7,77 (1H), 7,90+7,97 (1H) ppm.

Beispiel EL6

(1S,3S,7S,10R,11S,12S,16R)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) und (1R,3S,7S,10R,11S,12S,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

18 mg (22 µmol) der nach Beispiel EL5 dargestellten Verbindung setzt man in Analogie zu Beispiel EL2 um und isoliert nach Reinigung 9,2 mg (11,2 µmol, 51%) der Titelverbindung A sowie 3,2 mg (3,9 µmol, 18%) der Titelverbindung B jeweils als farblosen Schaum.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,98 (3H), 1,14 (3H), 1,16 (3H), 1,32 (3H), 1,03-1,67 (21H), 1,71-1,94 (3H), 2,18-2,78 (9H), 2,83 (3H), 3,50 (3H), 3,66 (1H), 3,87+4,43 (1H), 4,98 (1H), 5,04 (1H), 5,53 (1H), 5,69 (1H), 6,07 (1H), 6,68 (2H), 7,33 (1H), 7,80 (1H), 7,89+7,93 (1H) ppm.

^{1}H-NMR ($CDCl_3$) von B: δ = 0,80-1,64 (21H), 1,01 (3H), 1,03 (3H), 1,25 (3H), 1,33 (3H), 1,79-2,25 (5H), 2,34+3,14 (1H), 2,52-2,76 (4H), 2,81 (3H), 2,91 (1H), 3,40 (1H), 3,51 (2H), 3,67+3,82 (1H), 4,13+4,26 (1H), 4,46 (1H), 4,94 (1H), 5,01 (1H), 5,70 (1H), 5,81+5,94 (1H), 6,05+6,12 (1H), 6,68 (2H), 7,36 (1H), 7,74 (1H), 7,91+8,02 (1H) ppm.

Beispiel EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Beispiel EL7a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion

Die Lösung von 5,3 g (7,01 mmol) (4S,7R,8S,9S,13Z,16S)-7-Allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion, das man in Analogie zu dem in WO 00/66589 beschrieben Verfahren hergestellt hat, in einem Gemisch aus 85 ml Tetrahydrofuran und 85 ml Acetonitril versetzt man mit 31,7 ml Hexafluorkieselsäure, kühlt auf 0°C, tropft 8,1 ml Trifluoressigsäure zu und rührt 20 Stunden bei 0°C. Man gießt in Wasser, neutralisiert durch Zugabe einer gesättigten Natriumhydrogencarbonatlösung und extrahiert mehrfach mit Ethylacetat. Die vereinigten organischen Extrakte wäscht man mit gesättigter Natriumchloridlösung, trocknet über Natriumsulfat und reinigt den nach Filtration und Lösungsmittelabzug gewonnenen Rückstand durch Chromatographie an feinem Kieselgel. Isoliert werden 2,82 g (4,39 mmol, 63%) der Titelverbindung als farbloser Feststoff.

^{1}H-NMR ($CDCl_3$): δ = -0,09 (3H), 0,08 (3H), 0,84 (9H), 1,08 (3H), 1,10 (3H), 1,12 (3H), 1,21-1,86 (5H), 1,70 (3H), 2,15 (1H), 2,29-2,97 (8H), 2,84 (3H), 3,14 (1H), 3,96 (1H), 4,03 (1H), 4,97-5,06 (2H), 5,23 (1H), 5,61 (1H), 5,77 (1H), 7,35 (1H), 7,79 (1H), 7,93 (1H) ppm.

Beispiel EL7b

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) der nach Beispiel EL7a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1b mit dem nach Beispiel L4a hergestellten Linker um und isoliert nach Reinigung 121 mg (147 µmol, 94%) der Titelverbindung als farbloses Öl.

Beispiel EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

46 mg (56 µmol) der nach Beispiel EL7b dargestellten Verbindung setzt man in Analogie zu Beispiel EL1 um und isoliert nach Reinigung 17 mg (24 µmol, 43%) der Titelverbindung als farblosen Schaum.

^{1}H-NMR ($CDCl_3$): δ = 0,99-1,30 (2H), 1,03 (3H), 1,07 (3H), 1,21 (3H), 1,51-1,97 (6H), 1,72 (3H), 2,27-2,61 (6H), 2,83 (3H), 2,88 (1H), 3,09 (1H), 3,14 (2H), 3,51 (1H), 3,58 (2H), 4,04 (1H), 4,96-5,04 (2H), 5,12 (1H), 5,19 (1H), 5,28 (1H), 5,75 (1H), 5,86 (1H), 6,66 (2H), 7,35 (1H), 7,78 (1H), 7,96 (1H) ppm.

Beispiel EL8

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) und (1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (B)

29 mg (41 µmol) der nach Beispiel EL7 dargestellten Verbindung setzt man in Analogie zu Beispiel EL2 um und isoliert nach Reinigung 18 mg (24,9 µmol, 61%) der Titelverbindung A sowie 3,0 mg (4,1 µmol, 10%) der Titelverbindung B jeweils als farblosen Schaum.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,98 (3H), 1,05 (3H), 1,24 (3H), 1,26 (3H), 1,12-1,83 (9H), 2,12-2,46 (4H), 2,59 (2H), 2,76 (1H), 2,84 (3H), 3,14 (2H), 3,59 (3H), 3,98 (1H), 4,10 (1H), 4,95-5,02 (2H), 5,17 (2H), 5,77 (1H), 6,19 (1H), 6,70 (2H), 7,38 (1H), 7,82 (1H), 7,97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) von B: δ = 0,96 (3H), 1,01 (3H), 1,13-1,86 (11H), 1,28 (3H), 1,32 (1H), 2,16-2,50 (6H), 2,84 (3H), 3,02 (1H), 3,15 (2H), 3,50 (1H), 3,61 (2H), 3,88 (1H), 4,19 (1H), 4,96-5,04 (2H), 5,13 (1H), 5,28 (1H), 5,78 (1H), 6,33 (1H), 6,71 (2H), 7,36 (1H), 7,81 (1H), 7,96 (1H) ppm.

Beispiel EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-

carbaminsäure-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Beispiel EL9a

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) der nach Beispiel EL7a dargestellten Verbindung setzt man in Analogie zu Beispiel EL1b mit dem nach Beispiel L5a hergestellten Linker um und isoliert nach Reinigung 56 mg (65,9 µmol, 42%) der Titelverbindung als farbloses Öl.

Beispiel EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

56 mg (65,9 µmol) der nach Beispiel EL7b dargestellten Verbindung setzt man in Analogie zu Beispiel EL1 um und isoliert nach Reinigung 24,7 mg (33,6 µmol, 51%) der Titelverbindung als farblosen Schaum.

^{1}H-NMR ($CDCl_3$): δ = 0,97-1,84 (11H), 1,02 (3H), 1,07 (3H), 1,20 (3H), 1,71 (3H), 1,91 (1H), 2,27-2,57 (6H), 2,84 (3H), 2,88 (1H), 2,95 (1H), 3,16 (2H), 3,51 (3H), 4,02 (1H), 4,46+4,83 (1H), 4,94-5,03 (2H), 5,15 (1H), 5,20 (1H), 5,74 (1H), 5,84 (1H), 6,68 (2H), 7,35 (1H), 7,80 (1H), 7,96 (1H) ppm.

Beispiel EL10

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) und (1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (B)

24,7 mg (33,6 µmol) der nach Beispiel EL9 dargestellten Verbindung setzt man in Analogie zu Beispiel EL2 um und isoliert nach Reinigung 16,7 mg (22,2 µmol, 66%) der Titelverbindung A sowie 2,0 mg (2,7 µmol, 8%) der Titelverbindung B jeweils als farblosen Schaum.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,98 (3H), 1,04 (3H), 1,10-1,75 (13H), 1,23 (3H), 1,26 (3H), 2,09-2,62 (6H), 2,75 (1H), 2,84 (3H), 3,15 (2H), 3,51 (2H), 3,57 (1H), 3,99 (1H), 4,08 (1H), 4,46+4,74 (1H), 4,93-5,02 (2H), 5,18 (1H), 5,76 (1H), 6,18 (1H), 6,68 (2H), 7,38 (1H), 7,82 (1H), 7,97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) von B: δ = 0,83-1,85 (13H), 0,95 (3H), 1,01 (3H), 1,27 (3H), 1,32 (3H), 2,17-2,49 (6H), 2,84 (3H), 3,03 (1H), 3,17 (2H), 3,48 (1H), 3,53 (2H), 3,86 (1H), 4,18 (1H), 4,66 (1H), 4,94-5,03 (2H), 5,27 (1H), 5,76 (1H), 6,33 (1H), 6,69 (2H), 7,35 (1H), 7,81 (1H), 7,96 (1H) ppm.

Beispiel EL11

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbaminsäure 7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester

10 mg (19,7 µmol) (1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadecan setzt man in Analogie zu Beispiel EL1b mit dem nach Beispiel L4a hergestellten Linker um und isoliert nach Reinigung 7 mg (8,06 µmol, 41%) der Titelverbindung als farbloses Öl.

^{1}H-NMR ($CDCl_3$): δ = 0,88-2,20 (13H), 1,03 (3H), 1,05 (3H), 1,10 (3H), 1,24 (3H), 1,28 (3H), 2,08 (3H), 2,63-2,85 (4H), 2,71 (3H), 2,99-3,25 (3H), 3,41-3,50 (3H), 3,62 (2H), 4,88-5,70 (5H), 6,52 (1H), 6,69 (2H), 6,71 (2H), 7,02 (1H) ppm.

Beispiel EL12

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Beispiel EL12a

(4S,7R,8S,9S,13Z,16S)-Chlorameisensäure-7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Die Lösung von 1,0 g (1,56 mmol) der nach Beispiel EL1a dargestellten Verbindung in 20 ml Dichlormethan versetzt man bei 0°C mit der Lösung von 285 mg Triphosgen in 6 ml Dichlormethan, 160 µl Pyridin und rührt 2,5 Stunden bei 23°C. Man engt ein, nimmt den Rückstand in Ethylacetat auf, wäscht mit Wasser und gesättigter Natriumchloridlösung und trocknet über Magnesiumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an feinem Kieselgel. Isoliert werden 1,08 g (1,53 mmol, 98%) der Titelverbindung.

Beispiel EL12b

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Die Lösung von 267 mg (370 µmol) der nach Beispiel EL12a dargestellten Verbindung in 16 ml Ethylacetat versetzt man mit 51 µl Triethylamin, 700 mg der nach Beispiel L8 dargestellten Verbindung und rührt 16 Stunden bei 23°C. Man gießt in Wasser, extrahiert mehrfach mit Ethylacetat, wäscht die vereinigten organischen Extrakte mit gesättigter Natriumchloridlösung und trocknet über Magnesiumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an feinem Kieselgel. Isoliert werden 188 mg (219 µmmol, 59%) der Titelverbindung.

Beispiel EL12

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

In Analogie zu Beispiel EL1 setzt man 248 mg (289 µmol) der nach Beispiel EL12a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 149 mg (201 µmol, 69%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,08 (3H), 1,14 (3H), 1,26 (3H), 1,04-1,90 (8H), 2,24-2,57 (6H), 2,68-2,99 (3H), 2,81 (3H), 3,45 (1H), 3,72 (1H), 5,02 (1H), 5,06 (1H), 5,17 (1H), 5,65 (1H), 5,74 (1H), 5,98 (1H), 6,79 (2H), 6,88 (2H), 7,21 (2H), 7,33 (1H), 7,64 (1H), 7,97 (1H) ppm.

Beispiel EL13

(1S,3S,7S,10R,11S,12S,16R)-Kohlensäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

In Analogie zu Beispiel EL2 setzt man 144 mg (194 µmol) der nach Beispiel EL12 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 89 mg (117 µmol, 60%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,10 (3H), 1,14 (3H), 1,27 (3H), 1,32 (3H), 1,19-1,85 (7H), 2,08-2,89 (8H), 2,81 (3H), 3,50 (1H), 3,70 (1H), 5,02 (1H), 5,07 (1H), 5,58 (1H), 5,72 (1H), 6,10 (1H), 6,81 (2H), 6,88 (2H), 7,21 (2H), 7,31 (1H), 7,68 (1H), 7,93 (1H) ppm.

Beispiel EL14

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Beispiel EL14a

(4S,7R,8S,9S,13Z,16S)-Chlorameisensäure-7-allyl-4-(*tert*-butyl-dimethyl-

silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

In Analogie zu Beispiel EL12a setzt man 1,0 g (1,56 mmol) der nach Beispiel EL7a dargestellten Verbindung um und isoliert 1,05 g (1,49 mmol, 96%) der Titelverbindung.

Beispiel EL14b

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Die Lösung von 313 mg (0,44 mmol) der nach Beispiel EL14a dargestellten Verbindung in 19 ml Ethylacetat versetzt man mit 840 mg der nach Beispiel L8 dargestellten Verbindung, 61,5 µl Triethylamin und rührt 16 Stunden bei 23°C. Man versetzt mit Wasser, extrahiert mehrfach mit Ethylacetat, wäscht die vereinigten organischen Extrakte mit gesättigter Natriumchloridlösung und trocknet über Natriumsulfat. Den nach Filtration und Lösungsmittelabzug erhaltenen Rückstand reinigt man durch Chromatographie an feinem Kieselgel. Isoliert werden 298 mg (348 µmol, 79%) der Titelverbindung.

Beispiel EL14

(4S,7R,8S,9S,13Z,16S)-Kohlensäure 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

In Analogie zu Beispiel EL1 setzt man 304 mg (355 µmol) der nach Beispiel EL14a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 67 mg (90 µmol, 25%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,09 (3H), 1,11 (3H), 0,84-2,02 (7H), 1,27 (3H), 1,72 (3H), 2,29-2,58 (6H), 2,84 (3H), 2,89 (1H), 2,96 (1H), 3,63 (1H), 4,03 (1H), 5,06 (2H), 5,23 (2H), 5,80 (1H), 5,85 (1H), 6,86 (2H), 7,30 (2H), 7,35 (1H), 7,39 (1H), 7,80 (1H), 7,96 (1H) ppm.

Beispiel EL15

(1S,3S,7S,10R,11S,12S,16R)-Kohlensäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

In Analogie zu Beispiel EL2 setzt man 67 mg (90 µmol) der nach Beispiel EL14 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 32 mg (42 µmol, 47%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,05 (3H), 1,06 (3H), 1,25 (3H), 1,35 (3H), 1,21-1,90 (7H), 2,18 (2H), 2,33-2,67 (4H), 2,73 (1H), 2,85 (3H), 3,79 (1H), 4,11 (1H), 4,33 (1H), 5,02 (1H), 5,07 (1H), 5,31 (1H), 5,81 (1H), 6,27 (1H), 6,86 (2H), 7,29 (2H), 7,35-7,41 (3H), 7,83 (1H), 7,99 (1H) ppm.

Beispiel EL16

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-methyltrisulfanyl-*N*-methyl-propionamide

Die Lösung von 7 mg (13 µmol) (1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dion, das man in Analogie zu dem in WO 99/01124 beschriebenen Verfahren hergestellt hat, in 0,5 ml Dichlormethan versetzt mit 7 mg der nach Beispiel L1 dargestellten Verbindung, gibt 0,4 mg 4-Dimethylaminopyridin und 4 mg N,N'-Dicyclohexylcarbodiimid zu und rührt 20 Minuten bei 23°C. Man filtriert von ausgefallenem Harnstoff und reinigt durch Chromatographie an einer präparativen Dünnschichtplatte. Isoliert werden 5 mg (6,5 µmol, 50%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,00 (3H), 1,08 (3H), 1,17 (3H), 1,23-1,77 (5H), 1,28 (3H), 1,36 (3H), 1,39 (3H), 1,88-2,13 (3H), 2,10 (3H), 2,37 (1H), 2,49-2,66 (2H), 2,55 (3H), 2,77-2,92 (4H), 2,97 (3H), 3,16 (2H), 3,31 (1H), 3,77 (1H), 4,08 (1H), 4,19 (1H), 4,62 (1H), 4,76 (1H), 5,25 (1H), 5,45 (1H), 6,57 (1H), 7,01 (1H), 7,06 (1H) ppm.

Beispiel EL17

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-methyltrisulfanyl-propionyl)-amino]-propionsäure-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

In Analogie zu Beispiel EL 16 setzt man 10 mg (19 µmol) (1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0] heptadecane-5,9-dion, das man in Analogie zu dem in WO 99/01124 beschriebenen Verfahren hergestellt hat, um und isoliert 2,2 mg (2,8 µmol, 15%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,01 (3H), 1,09 (3H), 1,18 (3H), 1,27 (1H), 1,28 (3H), 1,32-1,76 (3H), 1,37 (3H), 1,47 (3H), 1,95 (1H), 2,06 (1H), 2,12 (3H), 2,38 (1H), 2,51-2,63 (2H), 2,56 (3H), 2,78-2,92 (5H), 2,97+3,01 (3H), 3,13-3,35 (3H), 3,71 (1H), 3,77 (1H), 4,00 (1H), 4,18 (1H), 5,25 (1H), 5,39 (2H), 5,45 (1H), 6,60 (1H), 7,17 (1H) ppm.

Beispiel EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL18a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 200 mg (284 µmol) der nach Beispiel EL12a dargestellten Verbindung mit 770 mg der nach Beispiel L9 dargestellten

Verbindung um und isoliert nach Aufarbeitung und Reinigung 129 mg (129 µmol, 45%) der Titelverbindung.

Beispiel EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 129 mg (129 µmol) der nach Beispiel EL18a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 71 mg (80 µmol, 62%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 0,88-2,11 (11H), 1,02 (3H), 1,14 (3H), 1,71 (3H), 2,23-2,56 (6H), 2,63-2,71 (3H), 2,74 (3H), 2,97 (1H), 3,39 (1H), 3,68 (3H), 4,58 (1H), 4,78 (1H), 5,01 (1H), 5,05 (1H), 5,18 (1H), 5,56 (1H), 5,71 (1H), 5,97 (1H), 6,73 (2H), 7,19 (1H), 7,31 (1H), 7,36 (1H), 7,75 (1H), 7,77 (1H), 7,95 (1H) ppm.

Beispiel EL19

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 71 mg (80 µmol) der nach Beispiel EL18 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 41 mg (45 µmol, 57%) der Titelverbindung A sowie 12 mg (13 µmol, 17%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 1,04 (3H), 1,14 (3H), 1,16 (3H), 1,32 (3H), 1,34-1,84 (6H), 2,01-2,74 (12H), 2,78 (3H), 2,86 (1H), 3,44 (1H), 3,68 (3H), 4,56 (1H), 4,74 (1H), 5,01 (1H), 5,06 (1H), 5,47 (1H), 5,70 (1H), 6,07 (1H), 6,73 (2H), 7,20 (1H), 7,32 (1H), 7,36 (1H), 7,77 (1H), 7,81 (1H), 7,90 (1H) ppm.

Beispiel EL20

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL20a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 243 mg (345 µmol) der nach Beispiel EL12a dargestellten Verbindung mit 1 g der nach Beispiel L10 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 25 mg (24 µmol, 7%) der Titelverbindung.

Beispiel EL20

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 212 mg (206 µmol) der nach Beispiel EL20a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 117 mg (128 µmol, 62%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,01 (3H), 1,14 (6H), 1,04-2,78 (20H), 1,70 (3H), 2,74 (3H), 2,97 (1H), 3,39 (1H), 3,56 (2H), 3,68 (1H), 4,11 (1H), 4,58 (1H), 4,77 (1H), 5,00 (1H), 5,05 (1H), 5,18 (1H), 5,56 (1H), 5,71 (1H), 5,97 (1H), 6,69 (2H), 7,12 (1H), 7,29 (1H), 7,36 (1H), 7,75 (2H), 7,94 (1H) ppm.

Beispiel EL21

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-

dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 117 mg (128 µmol) der nach Beispiel EL20 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 63 mg (68 µmol, 53%) der Titelverbindung A sowie 19 mg (20 µmol, 16%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 1,03 (3H), 1,14 (3H), 1,15 (3H), 1,32 (3H), 1,07-2,75 (22H), 2,77 (3H), 2,86 (1H), 3,44 (1H), 3,55 (2H), 3,69 (1H), 4,55 (1H), 4,77 (1H), 5,01 (1H), 5,06 (1H), 5,47 (1H), 5,70 (1H), 6,08 (1H), 6,70 (2H), 7,14 (1H), 7,31 (1H), 7,35 (1H), 7,76 (1H), 7,80 (1H), 7,90 (1H) ppm.

Beispiel EL22

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL22a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 243 mg (345 µmol) der nach Beispiel EL12a dargestellten Verbindung mit 1,19 g der nach Beispiel L11 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 171 mg (155 µmol, 45%) der Titelverbindung.

Beispiel EL22

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 171 mg (155 µmol) der nach Beispiel EL22a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 108 mg (110 µmol, 71%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,02 (3H), 1,14 (6H), 0,88-2,56 (28H), 1,70 (3H), 2,63 (2H), 2,71 (1H), 2,74 (3H), 2,98 (1H), 3,39 (1H), 3,50 (2H), 3,69 (1H), 4,58 (1H), 4,77 (1H), 5,00 (1H), 5,05 (1H), 5,17 (1H), 5,56 (1H), 5,71 (1H), 5,97 (1H), 6,68 (2H), 7,11 (1H), 7,29 (1H), 7,36 (1H), 7,75 (1H), 7,76 (1H), 7,94 (1H) ppm.

Beispiel EL23

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 108 mg (110 µmol) der nach Beispiel EL22 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 65,9 mg (65,8 µmol, 60%) der Titelverbindung A sowie 19,8 mg (20 µmol, 18%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 1,04 (3H), 1,14 (3H), 1,15 (3H), 1,63 (3H), 0,92-1,85 (23H), 2,10-2,81 (9H), 2,77 (3H), 2,86 (1H), 3,45 (1H), 3,51 (2H), 3,69 (1H), 4,55 (1H), 4,74 (1H), 5,01 (1H), 5,06 (1H), 5,47 (1H), 5,70 (1H), 6,08 (1H), 6,68 (2H), 7,13 (1H), 7,31 (1H), 7,35 (1H), 7,77 (1H), 7,80 (1H), 7,90 (1H) ppm.

Beispiel EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-

4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL24a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 271 mg (385 µmol) der nach Beispiel EL14a dargestellten Verbindung mit 1,04 g der nach Beispiel L9 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 193 mg (193 µmol, 50%) der Titelverbindung.

Beispiel EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 193 mg (193 µmol) der nach Beispiel EL24a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 107 mg (120 µmol, 62%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,02 (3H), 1,07 (3H), 1,23 (3H), 0,97-2,13 (8H), 1,71 (3H), 2,28-2,54 (6H), 2,67 (2H), 2,84 (3H), 2,88 (1H), 2,95 (1H), 3,56 (1H), 3,67 (2H), 4,01 (1H), 4,93 (1H), 4,98 (1H), 5,17 (1H), 5,22 (3H), 5,70 (1H), 5,84 (1H), 6,72 (2H), 7,30 (1H), 7,34 (1H), 7,69 (1H), 7,80 (1H), 7,95 (1H), 8,13 (1H) ppm.

Beispiel EL25

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butansäure 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-

methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 102 mg (115 µmol) der nach Beispiel EL19 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 65 mg (72 µmol, 63%) der Titelverbindung A sowie 3 mg (3,3 µmol, 3%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,97 (3H), 1,04 (3H), 1,23 (3H), 1,31 (3H), 1,10-2,75 (18H), 2,85 (3H), 3,68 (2H), 3,71 (1H), 4,09 (1H), 4,28 (1H), 4,92 (1H), 4,97 (1H), 5,20 (2H), 5,23 (1H), 5,72 (1H), 6,26 (1H), 6,72 (2H), 7,30 (1H), 7,37 (1H), 7,68 (1H), 7,83 (1H), 7,98 (1H), 8,13 (1H) ppm.

Beispiel EL26

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL26a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 273 mg (387 µmol) der nach Beispiel EL14a dargestellten Verbindung mit 1,12 g der nach Beispiel L10 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 69 mg (67 µmol, 17%) der Titelverbindung.

Beispiel EL26

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 69 mg (67 µmol) der nach Beispiel EL26a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 26 mg (28 µmol, 42%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 0,93 (3H), 0,95 (3H), 1,16 (3H), 1,60 (3H), 0,98-2,61 (20H), 2,73 (3H), 2,77 (1H), 3,45 (3H), 3,83 (1H), 4,05 (1H), 4,83 (1H), 4,88 (1H), 5,05 (1H), 5,13 (3H), 5,62 (1H), 5,74 (1H), 6,61 (2H), 7,16 (1H), 7,26 (1H), 7,60 (1H), 7,70 (1H), 7,88 (1H), 8,03 (1H) ppm.

Beispiel EL27

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexansäure 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 38 mg (41 µmol) der nach Beispiel EL19 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 14 mg (15 µmol, 37%) der Titelverbindung A sowie 2 mg (2 µmol, 5%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,96 (3H), 1,03 (3H), 1,08-1,86 (13H), 1,23 (3H), 1,30 (3H), 2,16 (2H), 2,23-2,78 (7H), 2,83 (3H), 3,54 (2H), 3,71 (1H), 4,09 (1H), 4,27 (1H), 4,91 (1H), 4,96 (1H), 5,21 (3H), 5,72 (1H), 6,25 (1H), 6,69 (2H), 7,23 (1H), 7,36 (1H), 7,67 (1H), 7,82 (1H), 7,96 (1H), 8,11 (1H) ppm.

Beispiel EL28

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Beispiel EL28a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL12b setzt man 273 mg (387 µmol) der nach Beispiel EL14a dargestellten Verbindung mit 1,34 g der nach Beispiel L11 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 196 mg (178 µmol, 46%) der Titelverbindung.

Beispiel EL28

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel EL1 setzt man 196 mg (178 µmol) der nach Beispiel EL28a dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 100 mg (101 µmol, 57%) der Titelverbindung.

^{1}H-NMR ($CDCl_3$): δ = 1,03 (3H), 1,06 (3H), 1,23 (3H), 1,70 (3H), 0,99-1,81 (21H), 1,91 (1H), 2,27-2,53 (6H), 2,63 (2H), 2,83 (3H), 2,88 (1H), 2,95 (1H), 3,51 (2H), 3,56 (1H), 4,00 (1H), 4,92 (1H), 4,98 (1H), 5,13-5,26 (4H), 5,71 (1H), 5,83 (1H), 6,68 (2H), 7,23 (1H), 7,34 (1H), 7,67 (1H), 7,79 (1H), 7,95 (1H), 8,13 (1H) ppm.

Beispiel EL29

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) und 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecansäure 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

In Analogie zu Beispiel EL2 setzt man 100 mg (101 µmol) der nach Beispiel EL19 dargestellten Verbindung um und isoliert nach Aufarbeitung und Reinigung 21 mg (21 µmol, 21%) der Titelverbindung A sowie 2 mg (2 µmol, 2%) der Titelverbindung B.

^{1}H-NMR ($CDCl_3$) von A: δ = 0,97 (3H), 1,04 (3H), 1,23 (3H), 0,84-1,84 (24H), 1,71 (3H), 2,15 (2H), 2,23-2,68 (5H), 2,71 (1H), 2,83 (3H), 3,50 (2H), 3,71 (1H), 4,09 (1H), 4,27 (1H), 4,91 (1H), 4,96 (1H), 5,19 (2H), 5,23 (1H), 5,72 (1H), 6,26 (1H), 6,68 (2H), 7,23 (1H), 7,36 (1H), 7,66 (1H), 7,83 (1H), 7,97 (1H), 8,12 (1H) ppm.

Beispiele zur Synthese von Effektor-Linker-Erkennungseinheiten (ELE)

Beispiel ELE1

[3-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

Beispiel ELE1a

Reduktion eines Antikörperfragments mit endständigem Cystein

Ein einzelsträngiges Protein bestehend aus den variablen Domänen der schweren und leichten Antikörper Kette (single-chain Fv, scFv) der Aminosäurenabfolge EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWV RQAPGKGLEWVSSISGSSGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT AVYYCAKPFPYFDYWGQGTLVTVSSGDGSSGGSGGASEIVLTQSPGTLSLSPGE RATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYYASSRATGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQTGRIPPTFGQGTKVEIKGGGCA, das spezifisch die Fibronektin Domäne B (ED-B) erkennt und als AP39 bezeichnet wird, wird nach Reduktion des c-terminalen Cysteins zur Kopplung verwendet.

Zur Reduktion wird die Lösung von 661 µg Tri(2-carboxyethyl)phosphin-Hydrochlorid in 236 µl PBS mit der Lösung von 1,54mg AP39 in 1,12 ml PBS versetzt und für 1,5 Stunden bei 25°C inkubiert. Man entsalzt mit einer voräquilibrierten NAP5-Säule bei einer Beladung mit 450 µl AP39r und 50 µl PBS. Nach Elution mit 1 ml PBS isoliert man das reduzierte Antikörperfragment AP39r in einer Konzentration von 0,7 mg/ml.

Beispiel ELE1

(1S,3S,7S(3RS),10R,11S,12S,16R)-[3-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

Zu 400 µl der nach Beispiel ELE1a dargestellten Lösung des reduzierten Antikörperfragmentes gibt man 22,5 µl einer 1,38 mM Lösung des nach Beispiel EL2 dargestellten Effektor-Linker-Konjugates A in DMSO, versetzt mit 77,5 µl PBS und inkubiert bei 25°C für 1 Stunde. Man entsalzt mit einer voräquilibrierten NAP5-Säule bei einer Beladung mit 500 µl der Reaktionslösung. Nach Elution mit PBS isoliert man die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.
m/z (ber.): 26203,1 m/z (exp.): 26218 ± 20

Beispiel ELE2

(1S,3S,7S(3RS),10R,11S,12S,16R)-[5-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

In Analogie zu Beispiel ELE1 setzt man das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL4 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.
m/z (ber.): 26231,2 m/z (exp.): 26236 ± 20

Beispiel ELE3

(1S,3S,7S(3RS),10R,11S,12S,16R)-[10-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-decyl]-carbaminsäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

In Analogie zu Beispiel ELE1 setzt man das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL6 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.
m/z (ber.): 26301,4 m/z (exp.): 26303 ± 20

Beispiel ELE4

(1S,3S,7S,10R,11S(3RS),12S,16R)-[3-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-

yl)-propyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL8 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26203,2 m/z (exp.): 26206 ± 20

Beispiel ELE5

(1S,3S,7S,10R,11S(3RS),12S,16R)-[5-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbaminsäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL10 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26231,2 m/z (exp.): 26225 ± 20

Beispiel ELE6

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbaminsäure-7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester (A) und

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbaminsäure-11-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester (B)

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL11 dargestellten Effektor-Linker-Konjugat um und isoliert die Lösung der Titelverbindungen. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26347,3 m/z (exp.): 26358 ± 20

Beispiel ELE7

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-(AP39r)-disulfanyl-*N*-methyl-propionamid

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL16 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26173 m/z (exp.): 26174 ± 20

Beispiel ELE8

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-(AP39r)-disulfanyl-propionyl)-amino]-propionsäure-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL17 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26174 m/z (exp.): 26163 ± 20

Beispiel ELE9

(1S,3S,7S,10R,11S,12S,16R)-Kohlensäure-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL13 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26238 m/z (exp.): 26224 ± 20

Beispiel ELE10

(1S,3S,7S,10R,11S,12S,16R)-Kohlensäure-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL15 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26238 m/z (exp.): 26243 ± 20

Beispiel ELE11

4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butansäure 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL19 dargestellten Effektor-Linker-Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.

m/z (ber.): 26383 m/z (exp.): 26377 ± 20

Beispiel ELE12

4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butansäure 4-(1S,3S,7S,10R,11S,12S, 16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

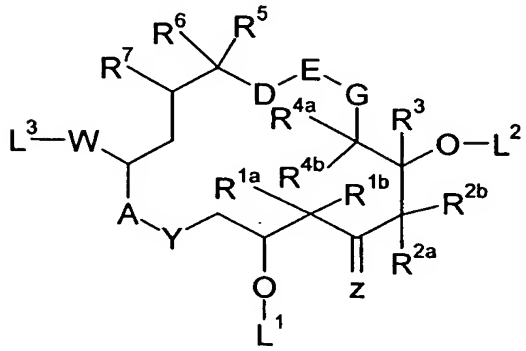
In Analogie zu Beispiel ELE1 setzt das nach Bespiel ELE1a reduzierte Antikörperfragment mit dem nach Beispiel EL25 dargestellten Effektor-Linker-

Konjugat A um und isoliert die Lösung der Titelverbindung. Der Verdünnungsfaktor bezogen auf das Antikörperfragment beträgt ca. 2,5.
m/z (ber.): 26383 m/z (exp.): 26381 ± 20

5

Patentansprüche

1. Effektor-Konjugat der allgemeinen Formel (I):



I,

worin

R^{1a}, R^{1b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_m$-Gruppe sind, worin m 2 bis 5 ist,

R^{2a}, R^{2b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_n$-Gruppe sind, worin n 2 bis 5 ist, oder C_2-C_{10} Alkenyl, oder C_2-C_{10} Alkinyl,

R^3 Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl, und

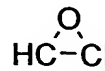
R^{4a}, R^{4b} unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, oder gemeinsam eine $-(CH_2)_p$-Gruppe sind, worin p 2 bis 5 ist,

R^5 Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, CO_2H, CO_2Alkyl, CH_2OH, CH_2OAlkyl, CH_2OAcyl, CN, CH_2NH_2, CH_2N(Alkyl, Acyl)$_{1,2}$, oder CH_2Hal,

Hal ein Halogen-Atom,

R^6, R^7 jeweils Wasserstoff, oder gemeinsam eine zusätzliche Bindung, oder gemeinsam ein Sauerstoff-Atom, oder gemeinsam eine NH-Gruppe, oder gemeinsam eine N-Alkyl-Gruppe, oder gemeinsam eine CH_2-Gruppe, und

G ein Sauerstoffatom oder CH_2 sind,

D-E eine Gruppe H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, oder, falls G eine CH_2-Gruppe darstellt, CH_2-O ist,

W eine Gruppe C(=X)R^8, oder ein bi- oder tricyclischer aromatischer oder heteroaromatischer Rest ist,

L^3 Wasserstoff ist, oder, falls ein Rest in W eine Hydroxyl-Gruppe enthält, mit dieser eine Gruppe O-L^4 bildet, oder, falls ein Rest in W eine Amino-Gruppe enthält, mit dieser eine Gruppe NR^{25}-L^4 bildet,

R^{25} Wasserstoff oder C_1-C_{10} Alkyl ist,

X ein Sauerstoffatom, oder zwei OR^{20}-Gruppen, oder eine C_2-C_{10} Alkylendioxy-Gruppe, die geradkettig oder verzeigt sein darf, oder H/OR^9, oder eine $CR^{10}R^{11}$-Gruppe,

R^8 Wasserstoff, C_1-C_{10} Alkyl, Aryl, Aralkyl, Halogen oder CN, und

R^9 Wasserstoff oder eine Schutzgruppe PG^X sind,

R^{10}, R^{11} jeweils unabhängig voneinander Wasserstoff, C_1-C_{20} Alkyl, Aryl, Aralkyl sind, oder gemeinsam mit einem Methylenkohlenstoffatom einen 5- bis 7-gliedrigen carbocyclischen Ring bilden,

Z Sauerstoff oder H/OR^{12},

R^{12} Wasserstoff oder eine Schutzgruppe PG^Z,

A-Y eine Gruppe O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) oder NR^{21}-SO_2,

R^{20} C_1-C_{20} Alkyl,

R^{21} ein Wasserstoffatom oder C_1-C_{10} Alkyl,

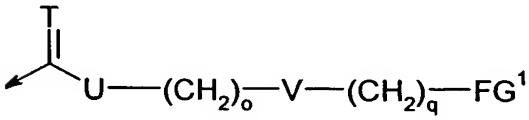
PG^X, PG^Y, PG^Z eine Schutzgruppe PG, und

L^1, L^2, L^4 unabhängig voneinander Wasserstoff, eine Gruppe C(=O)Cl, eine Gruppe C(=S)Cl, eine Gruppe PG^Y oder einen Linker der allgemeinen Formel (III) oder (IV)

darstellen können;

mit der Bedingung, dass mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel (III) oder (IV) darstellt;

der Linker der allgemeinen Formel (III) folgende Struktur hat,



III,

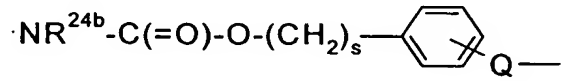
worin

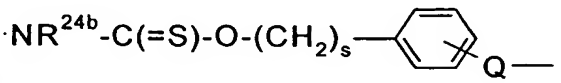
T Sauerstoff oder Schwefel,

U Sauerstoff, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)-, CHR^{22}-NR^{23}-C(=S)- oder NR^{24a},

o 0 bis 15,

V eine Bindung, Aryl,

eine Gruppe  oder

eine Gruppe  ,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion,

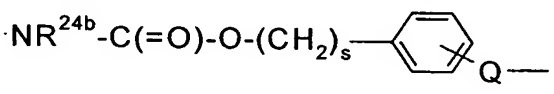
wobei an den in Formel (I) angegebenen Positionen die Wasserstoffatome in den vorstehend genannten Effektor-Grundkörpern durch Reste L^1-L^3 ersetzt sind.

4. Effektor-Konjugat gemäß einem der Ansprüche 1-3, wobei der Linker ausgewählt ist aus der Gruppe bestehend aus Verbindungen der allgemeinen Formel (III), wobei

   V eine Bindung oder einen Arylrest darstellt,
   o Null ist, und
   T ein Sauerstoffatom ist.

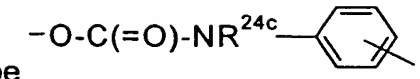
5. Effektor-Konjugat gemäß einem der Ansprüche 1-3, wobei der Linker ausgewählt ist aus der Gruppe bestehend aus Verbindungen der allgemeinen Formel (III), wobei

   V eine Bindung oder einen Arylrest oder eine Gruppe



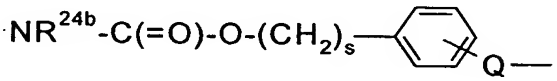
darstellt,

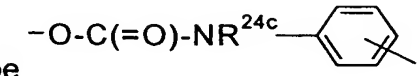
o 0 bis 4 ist, und

Q eine Bindung oder eine Gruppe  ist.

6. Effektor-Konjugat gemäß Anspruch 5, wobei

V eine Bindung oder eine Gruppe



Q eine Bindung oder eine Gruppe 

o 0, 2 oder 3,

s 1, und

T ein Sauerstoffatom ist.

7. Effektor-Konjugat gemäß einem der Ansprüche 1-3, wobei der Linker ausgewählt ist aus der Gruppe bestehend aus Verbindungen der allgemeinen Formel (IV), wobei

o 0 bis 4, und

q 0 bis 3 ist.

8. Effektor-Konjugat gemäß Anspruch 7, wobei

o 0, 2 oder 3,

W^1 Sauerstoff,

q 0,

R^{22} Wasserstoff, C_1-C_3 Alkyl oder Aralkyl,

R^{23} Wasserstoff oder C_1-C_3 Alkyl,

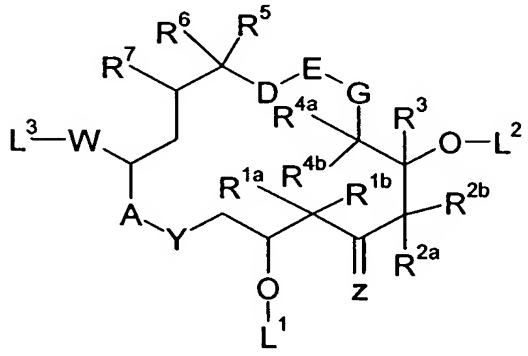
R^{24a} Wasserstoff oder C_1-C_3 Alkyl,

R^{27} Fluor, Chlor, CN, NO_2, CO_2R^{28} oder OR^{28},

R^{28} Wasserstoff oder C_1-C_5 Alkyl, und

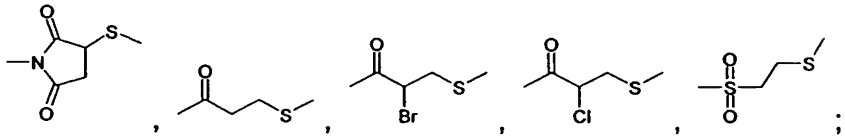
U Sauerstoff, CHR^{22}, oder CHR^{22}-NR^{23}-C(=O)- ist.

9. Effektor-Erkennungseinheit-Konjugat der allgemeinen Formel (I),



I,

wobei die Substituenten darin die in Anspruch 1 genannten Bedeutungen haben, jedoch mindestens eine Gruppe FG^1 durch eine Gruppe FG^{2a} oder FG^{2b} ersetzt ist, wobei FG^{2a} bzw. FG^{2b} die folgenden Bedeutungen haben können:

FG^{2a} -S-S-,  ;

FG^{2b} -CONH-;

und wobei eine Erkennungseinheit über ein Schwefelatom mit der Gruppe FG^{2a} oder über eine Amidfunktion mit der Gruppe FG^{2b} konjugiert ist;

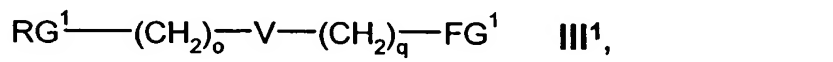
wobei die Erkennungseinheit ausgewählt ist aus der Gruppe bestehend aus Peptiden, löslichen Rezeptoren, Cytokinen, Lymphokinen, Aptameren, Spiegelmeren, rekombinanten Proteinen, neuen Framework-Strukturen, monoklonalen Antikörpern, und Fragmenten monoklonaler Antikörper;

als einheitliches Isomer oder eine Mischung unterschiedlicher Isomere und/oder als ein pharmazeutisch akzeptables Salz hiervon.

10. Effektor-Erkennungseinheit-Konjugat gemäß Anspruch 9, wobei das Konjugat mehr als eine Erkennungseinheit enthält, und wobei die Erkennungseinheiten identisch sind.

11. Effektor-Erkennungseinheit-Konjugat gemäß Anspruch 9 oder 10, wobei die Erkennungseinheit ein Antikörper ist, oder ein antigen-bindendes Fragment desselben, welcher für ein Antigen spezifisch ist, das ausgewählt ist aus der Gruppe bestehend aus den in Tabelle 1 aufgeführten Antigenen, sowie CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21, CD37, CD30, VCAM, CD31, ELAM, Endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), Phosphatidylserin, PSMA, VEGFR/VEGF-Komplex und ED-B-Fibronectin.

12. Linker der allgemeinen Formel (III^1):



$$RG^1\text{—}(CH_2)_o\text{—}V\text{—}(CH_2)_q\text{—}FG^1 \qquad III^1,$$

worin

RG^1 eine O=C=N-Gruppe oder eine S=C=N-Gruppe ist, und o, V, q und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (III^2):

$$RG^2\text{---}(CH_2)_o\text{---}V\text{---}(CH_2)_q\text{---}FG^1 \qquad III^2,$$

worin

RG^2 eine Hal-C(=T)-CHR^{22}-Gruppe oder eine Hal-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe ist, wobei R^{26} C_1-C_{10} Alkyl, Aryl, Aralkyl ist, und o, V, q und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (III^3):

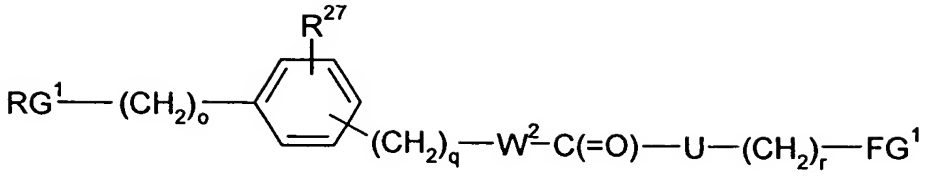
$$RG^3\text{---}(CH_2)_o\text{---}V\text{---}(CH_2)_q\text{---}FG^1 \qquad III^3,$$

worin

RG^3 eine OH-Gruppe oder eine NHR^{24a}-Gruppe oder eine COOH-Gruppe ist, und o, V, q und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

jedoch mit der Bedingung, dass die Verbindung 1-(4-Amino-phenyl)-pyrrol-2,5-dion nicht umfasst ist.

13. Linker der allgemeinen Formel (IV^1):

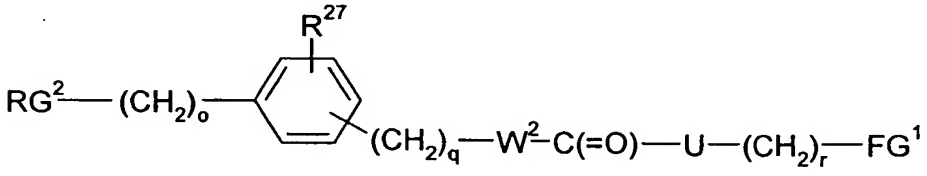


IV¹

worin

RG^1 eine O=C=N-Gruppe oder eine S=C=N-Gruppe ist, und o, q, r, W^2, R^{27}, U und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (IV^2):

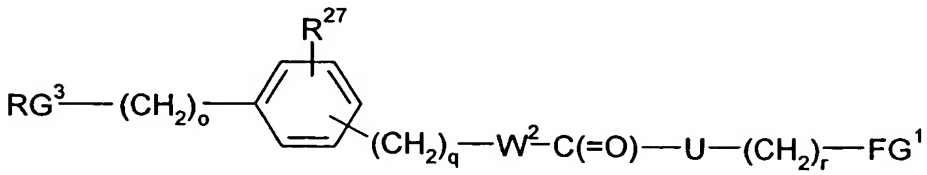


IV²

worin

RG^2 eine Hal-C(=T)-CHR^{22}-Gruppe oder eine Hal-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-Gruppe oder eine R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T)-Gruppe ist, wobei R^{26} C_1-C_{10} Alkyl, Aryl, Aralkyl ist, und R^{22}, R^{23}, T, o, q, r, W^2, R^{27}, U und FG^1 die in Anspruch 1 genannten Bedeutungen haben;

oder Linker der allgemeinen Formel (IV^3):



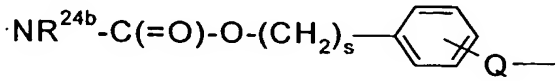
IV³

worin

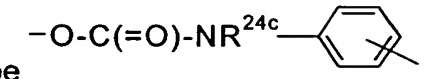
RG^3 eine OH-Gruppe oder eine NHR^{24a}-Gruppe oder eine COOH-Gruppe ist, und R^{24}, o, q, r, W^2, R^{27}, U und FG^1 die in Anspruch 1 genannten Bedeutungen haben.

14. Linker gemäß Anspruch 12, wobei V eine Bindung oder einen Arylrest darstellt, o gleich Null ist und T ein Sauerstoffatom ist.

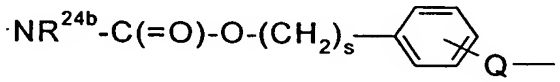
15. Linker gemäß Anspruch 12, wobei

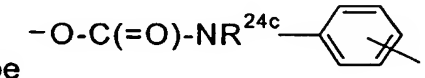
V eine Bindung oder einen Arylrest oder eine Gruppe  darstellt,

o 0 bis 4 ist, und

Q eine Bindung oder eine Gruppe  ist.

16. Linker gemäß Anspruch 15, wobei

V eine Bindung oder eine Gruppe  ,

Q eine Bindung oder eine Gruppe  ,

o 0, 2 oder 3,

s 1, und

T ein Sauerstoffatom ist.

17. Linker gemäß Anspruch 13, wobei

o 0 bis 4, und

q 0 bis 3 ist.

18. Linker gemäß Anspruch 17, wobei

o 0, 2 oder 3,

W^1 Sauerstoff,

q 0,

R^{22} Wasserstoff, C_1-C_3 Alkyl oder Aralkyl,

R^{23} Wasserstoff oder C_1-C_3 Alkyl,

R^{24a} Wasserstoff oder C_1-C_3 Alkyl,

R^{27} Fluor, Chlor, CN, NO_2, CO_2R^{28} oder OR^{28},

R^{28} Wasserstoff oder C_1-C_5 Alkyl, und

U Sauerstoff, CHR^{22}, oder CHR^{22}-NR^{23}-C(=O)- ist.

19. Verfahren zur Herstellung von Effektor-Konjugaten gemäß einem der Ansprüche 1-8, wobei eine Verbindung der allgemeinen Formel (I), wobei die Substituenten die in Anspruch 1 genannten Bedeutungen haben, jedoch

die Bedingung, das mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel (III) oder (IV) darstellt, nicht erfüllt sein muß, und mindestens ein Substituent L^1, L^2 oder L^4 Wasserstoff, eine Gruppe C(=O)Cl, oder eine Gruppe C(=S)Cl darstellt;

mit einem Linker, der ausgewählt ist aus der Gruppe bestehend aus einem Linker der allgemeinen Formel (III^1), (III^2), (III^3), (IV^1), (IV^2) oder (IV^3), wie in den Ansprüchen 12 bis 18 beschrieben, umgesetzt wird.

20. Verfahren zur Herstellung von Effektor-Erkennungseinheit-Konjugaten gemäß einem der Ansprüche 9 bis 11, wobei ein Effektor-Konjugat gemäß einem der Ansprüche 1-8 mit mindestens einer Erkennungseinheit, wie in Anspruch 9 und 11 definiert, umgesetzt wird.

21. Verwendung einer Verbindung der allgemeinen Formel (I), wobei die Substituenten die in Anspruch 1 genannten Bedeutungen haben, jedoch
die Bedingung, dass mindestens ein Substituent L^1, L^2 oder L^4 einen Linker der allgemeinen Formel (III) oder (IV) darstellt, nicht erfüllt sein muß, und mindestens ein Substituent L^1, L^2 oder L^4 Wasserstoff, eine Gruppe C(=O)Cl, oder eine Gruppe C(=S)Cl darstellt;
in einem Verfahren gemäß Anspruch 19.

22. Verwendung einer Verbindung der allgemeinen Formel (I) zur Herstellung eines Effektor-Erkennungseinheit-Konjugats gemäß den Ansprüchen 9 bis 11.

23. Verwendung eines Linkers der allgemeinen Formel (III^1), (III^2), (III^3), (IV^1), (IV^2) oder (IV^3) in einem Verfahren gemäß Anspruch 19.

24. Verwendung eines Linkers der allgemeinen Formel (III^1), (III^2), (III^3), (IV^1), (IV^2) oder (IV^3) zur Herstellung eines Effektor-Erkennungseinheit-Konjugats gemäß einem der Ansprüche 9 bis 11.

25. Verwendung einer Erkennungseinheit, wie in Anspruch 9 oder 11 definiert, in einem Verfahren gemäß Anspruch 20.

26. Effektor-Erkennungseinheit-Konjugat gemäß einem der Ansprüche 9 bis 11 zur Verwendung als Medikament.

27. Effektor-Erkennungseinheit-Konjugat gemäß einem der Ansprüche 9 bis 11 zur Verwendung als Medikament zur Behandlung von Erkrankungen, die mit proliferativen Prozessen assoziiert sind.

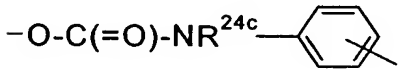
28. Effektor-Erkennungseinheit-Konjugat gemäß einem der Ansprüche 9 bis 11 zur Verwendung als Medikament zur Behandlung einer Krankheit, die ausgewählt ist aus der Gruppe bestehend aus Tumoren, entzündlichen Erkrankungen, neurodegenerativen Erkrankungen, Angiogenese-assoziierten Erkrankungen, Multipler Sklerose, Alzheimer, und rheumatoider Arthritis.

Zusammenfassung:

Konjugate von Epothilonen und Epothilonderivaten (als Effektoren) mit geeigneten Biomolekülen (als Erkennungseinheiten) werden beschrieben. Ihre Herstellung erfolgt, indem die Effektoren mit geeigneten Linkern umgesetzt werden und die entstehenden Verbindungen an die Erkennungseinheiten konjugiert werden. Die pharmazeutische Verwendung der Konjugate zur Behandlung von proliferativen oder Angiogenese-assoziierten Prozessen wird beschrieben.

s 0 bis 4,

Q eine Bindung, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c},

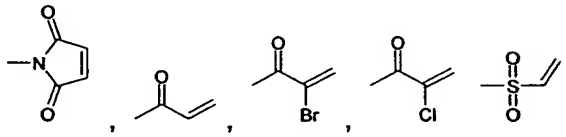

oder

R^{22} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl

R^{23} Wasserstoff oder C_1-C_{10} Alkyl,

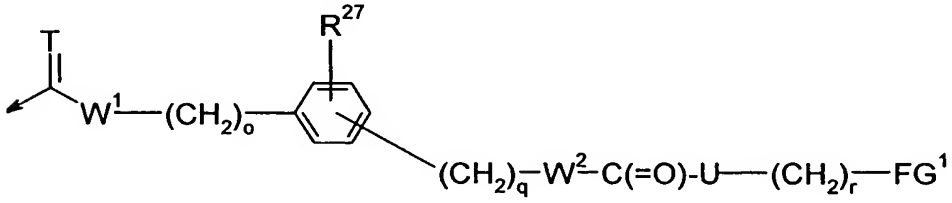
R^{24a}, R^{24b}, R^{24c} unabhängig voneinander Wasserstoff oder C_1-C_{10} Alkyl,

q 0 bis 15,

FG^1 C_1-C_{10} Alkyl-S_3-,  oder CO_2H

darstellen können; und

der Linker der allgemeinen Formel (IV) folgende Struktur hat,


IV,

worin

T Sauerstoff oder Schwefel,

W^1, W^2 gleich oder verschieden sind und Sauerstoff oder NR^{24a},

o 0 bis 5,

R^{24a} Wasserstoff oder C_1-C_{10} Alkyl,

R^{27} Halogen, CN, NO_2, CO_2R^{28}, OR^{28},

R^{28} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl

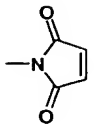
q 0 bis 5,

U Sauerstoff, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-, oder C_1-C_{20} Alkyl,

R^{22} Wasserstoff, C_1-C_{10} Alkyl, Aryl oder Aralkyl,

R^{23} Wasserstoff oder C_1-C_{10} Alkyl,

r 0 bis 20,

FG^1 C_1-C_{10} Alkyl-S_3,  ,  ,  ,  , 
oder CO_2H,

darstellen können;

als einheitliches Isomer oder eine Mischung unterschiedlicher Isomere und/oder als ein pharmazeutisch akzeptables Salz hiervon.

2. Effektor-Konjugat gemäß Anspruch 1, wobei:

A-Y	O-C(=O) oder NR^{21}-C(=O),
D-E	eine H_2C-CH_2-Gruppe,
G	eine CH_2-Gruppe,
Z	ein Sauerstoffatom,
R^{1a}, R^{1b}	jeweils C_1-C_{10} Alkyl oder zusammen eine $-(CH_2)_p$-Gruppe mit p gleich 2 oder 3 oder 4,
R^{2a}, R^{2b}	unabhängig voneinander Wasserstoff, C_1-C_{10} Alkyl, C_2-C_{10} Alkenyl, oder C_2-C_{10} Alkinyl,
R^3	Wasserstoff;
R^{4a}, R^{4b}	unabhängig voneinander Wasserstoff oder C_1-C_{10} Alkyl;
R^5	Wasserstoff, oder C_1-C_4 Alkyl oder CH_2OH oder CH_2NH_2 oder $CH_2N(Alkyl, Acyl)_{1,2}$ oder CH_2Hal,
R^6 und R^7	gemeinsam eine zusätzliche Bindung oder gemeinsam eine NH-Gruppe oder gemeinsam eine N-Alkyl-Gruppe oder

gemeinsam eine CH_2-Gruppe, oder gemeinsam ein Sauerstoffatom,

W eine Gruppe $C(=X)R^8$ oder ein 2-Methylbenzothiazol-5-yl-Radikal oder ein 2-Methylbenzoxazol-5-yl-Radikal oder ein Chinolin-7-yl-Radikal oder ein 2-Aminomethylbenzothiazol-5-yl-Radikal oder ein 2-Hydroxymethylbenzothiazol-5-yl-Radikal oder ein 2-Aminomethyl-benzoxazol-5-yl-Radikal oder ein 2-Hydroxymethylbenzoxazol-5-yl-Radikal,

X eine $CR^{10}R^{11}$-Gruppe

R^8 Wasserstoff oder C_1-C_4 Alkyl oder ein Fluoratom oder ein Chloratom oder ein Bromatom,

R^{10}/R^{11} Wasserstoff/2-Methylthiazol-4-yl oder Wasserstoff/2-Pyridyl oder Wasserstoff/2-Methyloxazol-4-yl oder Wasserstoff/2-Aminomethylthiazol-4-yl oder Wasserstoff/2-Aminomethyloxazol-4-yl oder Wasserstoff/2-Hydroxymethylthiazol-4-yl oder Wasserstoff/2-Hydroxymethyloxazol-4-yl

darstellen.

3. Effektor-Konjugat gemäß Anspruch 1 oder 2, wobei der Effektor-Grundkörper ausgewählt ist aus der Gruppe bestehend aus:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chlor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chlor-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chlor-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chlor-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-en-2,6-dion;
(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;
(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-en-2,6-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecan-5,9-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-en-2,6-dion;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-en-2,6-dion;

VERIFICATION OF TRANSLATION

I, Melissa Stanford, a translator with Chillson Translating Service, 3530 Chas Drive, Hampstead, Maryland, 21074, hereby declare as follows:

That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application 103 05 098.1 filed February 7, 2003 titled, "New Effector Conjugates, Process for their Production and their Pharmaceutical Use;"

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

And further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any registration resulting therefrom.

By Melissa Stanford

Executed this 6 day of Oct 2003.

Witness Anne Chillson

FEDERAL REPUBLIC OF GERMANY

Priority Certificate on the Filing of a Patent Application

File Number:	103 05 098.1
Date of Application:	February 7, 2003
Applicant/Holder:	Schering AG, Berlin/DE
Title:	New Effector Conjugates, Process for their Production and their Pharmaceutical Use
IPC:	C 07 D, C 07 K, A 61 K

The attached copies are a true and accurate rendition of the original documents of this patent application.

Munich, August 4, 2003

The German Patent and Trademark Office

The Director

/s/

Klostermeyer

Applicant: **Schering AG**

Our Ref.: **SCH10522DE2**

New Effector Conjugates, Process for their Production and their Pharmaceutical Use

The development of the understanding relating to the recognition of binding regions, especially to the field of monoclonal antibodies or fragments thereof against specific tumor antigens, makes it possible to consider a selective tumor therapy by specific release of an anti-tumor active ingredient at the target site.

A precondition for such an approach, in which a highly active (toxic) active ingredient (effector) is coupled to a high-molecular, tumor-specific recognition unit, such as, for example, to an antibody, is a substantial inactivity of the conjugate, whose minimum components produce a recognition unit and an effector until the latter has reached the target site (tumor). Arriving at the target site, the conjugate binds to the cell surface and the active ingredient, optionally after the preceding internalization of the entire complex, can be released.

The successful therapy of solid tumors, especially with monoclonal antibodies, can be limited, however, by an inadequate penetration of the antibody into the tumor as well as the heterogeneous dispersion of the corresponding tumor-associated antigen in the tumor tissue.

These limitations thus could be avoided in that the tumor-vascular system is attacked in a specific way. The growth of tumors below a volume of about 2 mm^3

depends on a neoangiogenesis. The additional tumor growth is based on an intact vascular system, which ensures the supply with nutrients or the removal of waste products. The selective destruction of this system should therefore result in a necrosis of the tumor. The attack on the vascular system of the tumor promises a number of advantages relative to the direct attack on the tumor itself. In comparison to tumor cells, endothelial cells are easier to access since no tumor tissue has to be penetrated. The damage of an individual tumor vessel should result in a necrosis of a thousand tumor cells. To damage a tumor vessel, it is not necessary to kill all endothelial cells. The specific attack of endothelial cells in or close to the tumors minimizes systemic side effects. Endothelial cells are genetically very stable, so that the probability of a development of resistance against the tumor therapeutic agent is low.

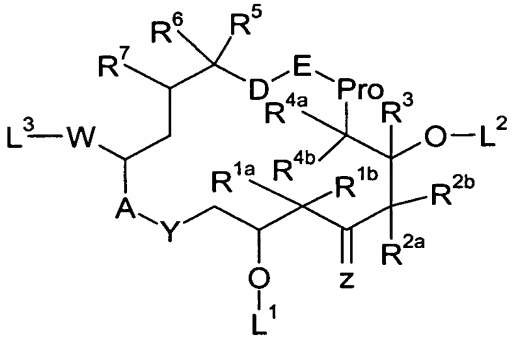
Within the scope of this invention, surprisingly enough, a possibility has now been found to link the chemically very sensitive, highly-functionalized active ingredient class of epothilones and analogs thereof to a high-molecular recognition unit via different linkers in different positions of the active ingredient.

The object of this invention is thus, i.a.,

1. To find a method to link highly active active ingredients from the structural class of the epothilones and epothilone derivatives with suitable linkers,
2. To synthesize suitable linkers,
3. To develop a method to link these epothilone-linker conjugates with recognition units, such as, for example, monoclonal antibodies or fragments thereof to immune conjugates that are both chemically and metabolically sufficiently stable for a pharmaceutical agent development and that are superior to the epothilones or epothilone derivatives that are taken as a basis with respect to their therapeutic

range, their selectivity of action and/or undesirable toxic side effects and/or their active strength.

This invention accordingly comprises effector conjugates of general formula I



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2OAlkyl, CH_2OAcyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7 in each case are hydrogen, or together an additional bond, or together an oxygen atom, or together an NH group, or together an N-alkyl group, or together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH), , O-CH_2, or, if G represents a CH_2 group, D-E is CH_2-O,

W is a group $C(=X)R^8$, or a bi- or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group that should be straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11} in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} can represent C_1-C_{20} alkyl,

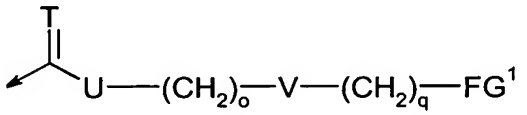
R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG, and

L^1, L^2, and L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker of general formula (III) or (IV);

provided that at least one substituent L^1, L^2 or L^4 represents a linker of general formula (III) or (IV);

the linker of general formula (III) has the following structure,



III,

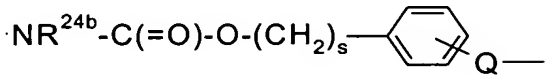
in which

T can represent oxygen or sulfur,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)- or NR^{24a},

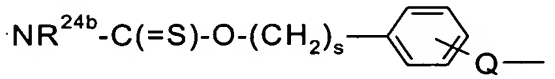
o can represent 0 to15,

V can represent a bond, aryl, a group



,

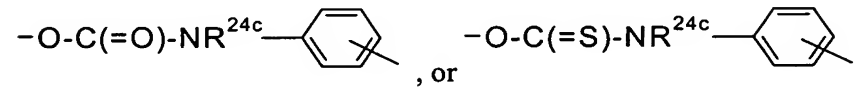
or a group



,

s can represent 0 to 4,

Q can represent a bond, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c},



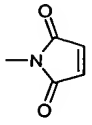
, or

R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

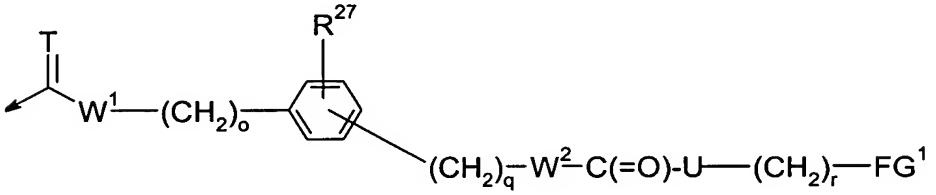
R^{23} can represent hydrogen or C_1-C_{10} alkyl,

R^{24a}, R^{24b}, and R^{24c}, independently of one another, can represent hydrogen or C_1-C_{10} alkyl,

q can represent 0 to 15,

FG^1 can represent C_1-C_{10} alkyl-S_3,  , ,  ,  ,  ,  , or CO_2H; and

the linker of general formula (IV) has the following structure,



IV,

in which

T can represent oxygen or sulfur,

W^1, W^2 are the same or different and can represent oxygen or NR^{24a},

o can represent 0 to 5,

R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen or C_1-C_{10} alkyl,

R^{24a} can represent hydrogen or C_1-C_{10} alkyl,

R^{27} can represent halogen, CN, NO_2, CO_2R^{28}, or OR^{28},

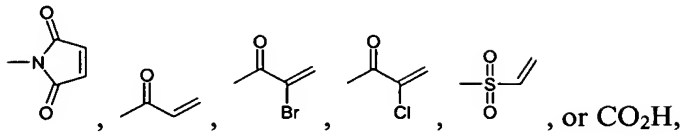
R^{28} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

q can represent 0 to 5,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)- or C_1-C_{20} alkyl,

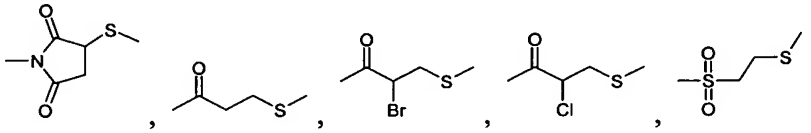
r can represent 0 to 20,

FG^1 can represent C_1-C_{10} alkyl-S_3,


, or CO_2H,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

In addition, the invention describes the production of effector recognition unit conjugates of general formula (I), whereby the substituents therein have the above-mentioned meanings, but at least one group FG^1 is replaced by a group FG^{2a} or FG^{2b}, whereby FG^{2a} or FG^{2b} can have the following meanings:

FG^{2a}: -S-S-, 

FG^{2b}: -CONH-

and whereby a recognition unit is conjugated via a sulfur atom with the group FG^{2a}, whereby the indicated sulfur atom is a component of the recognition unit, or via an amide function of group FG^{2b}, whereby the indicated nitrogen atom is a component of the recognition unit;

whereby the recognition unit can be, for example, a peptide, a soluble receptor, a cytokine, a lymphokine, an aptamer, a spiegelmer, a recombinant protein, a framework structure, a monoclonal antibody or a fragment of a monoclonal antibody.

According to this invention, the above-mentioned effector recognition unit conjugates can comprise one or more recognition units; in this case, the recognition units that correspond to a conjugate can be identical or different. It is preferred that the recognition units be identical to a conjugate.

The effector recognition unit conjugates according to the invention can be used in the form of their α-, β- or γ-cyclodextrin-clathrates or in the form of liposomal or pegylated compositions.

The conjugates according to the invention are preferably used for the treatment of diseases that are linked with proliferative processes. For example, the therapy of the most varied tumors, the therapy of inflammatory and/or neurodegenerative diseases, such as multiple sclerosis or Alzheimer's disease, the therapy of angiogenesis-associated diseases such as the growth of solid tumors, rheumatoid arthritis or diseases of the ocular fundus, can be mentioned.

The production of epothilones, their precursors and derivatives of general formula I is carried out according to the methods that are known to one skilled in the art, as they are described in, for example, DE 19907588, WO 98/25929, WO 99/58534, WO 99/2514, WO 99/67252, WO 99/67253, WO 99/7692, EP 99/4915, WO 00/485, WO 00/1333, WO 00/66589, WO 00/49019, WO 00/49020, WO 00/49021, WO 00/71521, WO 00/37473, WO 00/57874, WO 01/92255, WO 01/81342, WO 01/73103, WO 01/64650, WO 01/70716, US 6204388, US 6387927, US 6380394, US 02/52028, US 02/58286, US 02/62030, WO 02/32844, WO 02/30356, WO 02/32844, WO 02/14323, and WO 02/8440.

As alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3}, R^{4a}, R^{4b}, R^{5}, R^{8}, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} and R^{26}, straight-chain or branched-chain alkyl groups with 1-20 carbon atoms can be considered, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, and decyl.

Alkyl groups R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3}, R^{4a}, R^{4b}, R^{5}, R^{8}, R^{10}, R^{11}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24a}, R^{24b}, R^{24c}, R^{25} and R^{26} can also be perfluorinated or substituted by 1-

5 halogen atoms, hydroxy groups, C_1-C_4-alkoxy groups or C_6-C_{12}-aryl groups (which can be substituted by 1-3 halogen atoms).

As aryl radicals R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22}, R^{26} and V, substituted and unsubstituted carbocyclic or heterocyclic radicals with one or more heteroatoms, such as phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, benzothiazolyl or benzoxazolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized, provided that this does not cause the aromatic character to be lost, such as, for example, the oxidation of a pyridyl to a pyridyl-N-oxide.

As bicyclic and tricyclic aryl radicals W, substituted and unsubstituted, carbocyclic or heterocyclic radicals with one or more heteroatoms such as naphthyl, anthryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, benzoxazinyl, benzofuranyl, indolyl, indazolyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thienopyridinyl, pyridopyridinyl, benzopyrazolyl, benzotriazolyl, or dihydroindolyl, which can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NH_2$, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups, are suitable. The heteroatoms can be oxidized, provided that this does not cause the aromatic character to be lost, such as, for example, the oxidation of a quinolyl to a quinolyl-N-oxide.

The aralkyl groups in R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, R^5, R^8, R^{10}, R^{11}, R^{22} and R^{26} can contain in the ring up to 14 C atoms, preferably 6 to 10 C atoms, and in the alkyl chain 1 to 8 atoms, preferably 1 to 4 atoms. As an aralkyl radical, for example, benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl or

pyridylpropyl is suitable. The rings can be substituted in one or more places by halogen, OH, O-alkyl, CO_2H, CO_2-alkyl, $-NO_2$, $-N_3$, -CN, C_1-C_{20}-alkyl, C_1-C_{20}-acyl or C_1-C_{20}-acyloxy groups.

As representatives of protective groups PG, tris(C_1-C_{20} alkyl)silyl, bis(C_1-C_{20} alkyl)-arylsilyl, (C_1-C_{20} alkyl)-diarylsilyl, tris(aralkyl)-silyl, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_4-C_7-cycloalkyl, which in addition can contain an oxygen atom in the ring, aryl, C_7-C_{20}-aralkyl, C_1-C_{20}-acyl, aroyl, C_1-C_{20}-alkoxycarbonyl, C_1-C_{20}-alkylsulfonyl as well as arylsulfonyl can be cited.

As alkyl-, silyl- and acyl radicals for the protective groups PG, especially the radicals that are known to one skilled in the art are considered. Preferred are the alkyl or sily radicals that can be easily cleaved from the corresponding alkyl and silyl ethers, such as, for example, the methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert.-butyldimethylsilyl, tert.-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, and para-methoxybenzyl radicals, as well as alkylsulfonyl and arylsulfonyl radicals. As an alkoxycarbonyl radical, e.g., trichloroethyloxycarbonyl (Troc) is suitable. As an acyl radical, e.g., formyl, acetyl, propionyl, isopropionyl, trichloromethylcarbonyl, pivalyl, butyryl or benzoyl, which can be substituted with amino and/or hydroxy groups, is suitable.

As amino protective groups PG, the radicals that are known to one skilled in the art are suitable. For example, the alloc, boc, Z, benzyl, f-moc, troc, stabase or benzostabase group can be mentioned.

As halogen atoms, fluorine, chlorine, bromine or iodine can be considered.

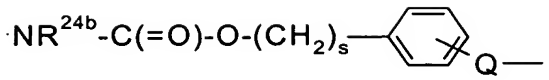
The acyl groups can contain 1 to 20 carbon atoms, whereby formyl, acetyl, propionyl, isopropionyl and pivalyl groups are preferred.

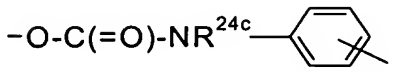
The C_2-C_{10}-alkylene-α,ω-dioxy group that is possible for X is preferably an ethylene ketal or neopentyl ketal group.

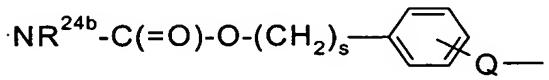
Preferred compounds of general formula I are those in which A-Y represents O-C(=O) or NR^{21}-C(=O); D-E represents an H_2C-CH_2 group; G represents a CH_2 group; Z represents an oxygen atom; R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4; R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl; R^3 represents hydrogen; R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl; R^5 represents hydrogen, or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal; R^6 and R^7 together represent an additional bond or together an NH group or together an N-alkyl group or together a CH_2 group or together an oxygen atom; W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethylbenzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical; X represents a $CR^{10}R^{11}$ group; R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom; R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

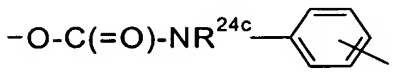
As linkers of general formula (III), compounds are preferred in which V represents a bond or an aryl radical, o is equal to zero, and T represents an oxygen atom.

As linkers of general formula (III), in addition compounds are preferred in which V represents a bond or an aryl radical or a group


; Q represents a bond or a group


; and o is 0 to 4. Especially preferred are compounds of general formula (III), whereby V represents a bond or a group


; Q represents a bond or a group


; o is equal to 0, 2 or 3; s is equal to 1; and T is an oxygen atom.

As linkers of general formula (IV), compounds are preferred in which o is zero to four, and q is zero to three. Especially preferred are compounds of general formula (IV), whereby o is 0, 2 or 3; W^1 is an oxygen atom; q is equal to 0; R^{22} is hydrogen, C_1–C_3 alkyl or aralkyl; R^{23} is hydrogen or C_1–C_3 alkyl; R^{24a} is hydrogen or C_1–C_3 alkyl; R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28}; R^{28} is hydrogen or C_1–C_5 alkyl; and U is oxygen, CHR^{22} or CHR^{22}–NR^{23}–C(=O)-.

As recombinant proteins for use as recognition units, for example, binding regions derived from antiodies, so-called CDRs, are suitable.

As framework structures for use as recognition units, for example, high-molecular structures that are not derived from antibodies are suitable. For example, structures such as fibronectin-type 3 and crystallins can be mentioned.

As fragments of monoclonal antibodies for use as recognition units, for example, single-chain Fv, Fab, $F(ab)_2$ as well as recombinant multimers can be mentioned.

As preferred recognition units, those are considered that are suitable for, for example, the recognition and/or diagnosis and/or therapy of solid tumors and malignant diseases of the hematopoietic system.

As recognition units that are preferred in addition, those are considered that make possible a selective recognition of the disease-specific vascular system, preferably angiogenesis.

Table 1 cites examples of especially preferred recognition units for treating solid tumors.

TABLE 1

Tumor	**Antigen Identity/ Characteristics**	**Monoclonal Antibodies**	**References**
Gynecol. (GY)	CA 125' > 200 kD mucin GP	OC 125	Kabawat et al., 1983; Szymendera, 1986
Ovarian	80 Kd GP	OC 133	Masuko et al., Cancer Res, 1984
Ovarian	'SGA' 360 Kd GP	OMI	de Krester et al., 1986
Ovarian	High M_r mucin	Mo v1	Miotti et al., Cancer Res, 1985
Ovarian	High M_r mucin/ glycolipid	Mo v2	Miotti et al., Cancer Res, 1985
Ovarian	NS	3C2	Tsuji et al., Cancer Res, 1985

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Ovarian	NS	4C7	Tsuji et al., Cancer Res, 1985
Ovarian	High M_r mucin	ID3	Gangopadhyay et al., 1985
Ovarian	High M_r mucin	DU-PAN-2	Lan et al., 1985
GY	7700 Kd GP	F 36/22	Croghan et al., 1984
Ovarian	'gp 68' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
GY	40, 42kD GP	OV-TL3	Poels et al., 1986
GY	'TAG-72' High M_r mucin	B72.3	Thor et al., 1986
Ovarian	300-400 Kd GP	DF_3	Kufe et al., 1984
Ovarian	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985
GY	105 Kd GP	MF 116	Mattes et al., 1984
Ovarian	38-40 kD GP	Mov18	Miotti et al., 1987
GY	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Ovarian	CA 19-9 or GICA	CA 19-9 (1116NS 19-9)	Atkinson et al., 1982
Ovarian	'FLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Ovarian	72 Kd	791T/36	Perkins et al., 1985
Ovarian	69 Kd PLAP	$NDOG_2$	Sunderland et al., 1984
Ovarian	unknown M_r PLAP	H317	Johnson et al., 1981

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Ovarian	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
Uterus, Ovary	HMFG-2	HMFG2	Epenetos et al., 1982
GY	HMFG-2	3.14.A3	Burchell et al., 1983
Breast	330-450 Kd GP	DF3	Hayes et al., 1985
Breast	NS	NCRC-11	Ellis et al., 1984
Breast	37kD	3C6F9	Mandeville et al., 1987
Breast	NS	MBE6	Teramoto et al., 1982
Breast	NS	CLNH5	Glassy et al., 1983
Breast	47 Kd GP	MAC 40/43	Kjeldsen et al., 1986
Breast	High M_r GP	EMA	Sloane et al., 1981
Breast	High M_r GP	HMFG1 HFMG2	Arklie et al., 1981
Breast	NS	3.15.C3	Arklie et al., 1981
Breast	NS	M3, M8, M24	Foster et al., 1982
Breast	1 (Ma) Blood Group Ags	M18	Foster et al., 1984
Breast	NS	67-D-11	Rasmussen et al., 1982
Breast	Estrogen Receptor	D547Sp, D75P3, H222	Kinsel et al., 1989
Breast	EGF Receptor	Anti EGF	Sainsbury et al., 1985

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Breast	Laminine Receptor	LR-3	Horan Hand et al., 1985
Breast	*erb* B-2 p185	TA1	Gusterson et al., 1988
Breast	NS	H59	Hendler et al., 1981
Breast	126 Kd GP	10-3D-2	Soule et al., 1983
Breast	NS	HmAB1,2	Imam et al., 1984; Schlom et al., 1985
Breast	NS	MBR 1,2,3	Menard et al., 1983
Breast	95 Kd	24-17-1	Thompson et al., 1983
Breast	100 Kd	24-17-2 (3E1-2)	Croghan et al., 1983
Breast	NS	F36/22.M7/105	Croghan et al., 1984
Breast	24 Kd	C11, G3, H7	Adams et al., 1983
Breast	90 Kd GP	B6-2	Colcher et al., 1981
Breast	CEA & 180 Kd GP	B1-1	Colcher et al., 1983
Breast	Colon & pancreas, mucin-like Ca 19-9	Cam 17-1	Imperial Cancer Research Technology MAb listing
Breast	Milk mucin, nuclear protein	SM3	Imperial Cancer Research Technology Mab listing
Breast	Milk mucin, nuclear protein	SM4	Imperial Cancer Research Technology Mab listing

Tumor	**Antigen Identity/ Characteristics**	**Monoclonal Antibodies**	**References**
Breast	Affinity-purified milk mucin	C-Mul (566)	Imperial Cancer Research Technology Mab listing
Breast	$P185^{HER2}$	4D5 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, 5B8	Shepard et al., 1991
Breast	CA 125 > 200 Kd GP	OC 125	Kabawat et al., 1985
Breast	High M_r mucin/ glycolipid	MO v2	Miotti et al., 1985
Breast	High M_r mucin	DU-PAN-2	Lan et al., 1984
Breast	'gp48' 48 Kd GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Breast	300-400 Kd GP	DF_3	Kufe et al., 1984
Breast	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986
Breast	'CEA' 180 Kd GP	ccccCEA 11	Wagener et al., 1984
Breast	'PLAP' 67 Kd GP	H17-E2	McDicken et al., 1985
Breast	HMFG-2 > 400 Kd GP	3-14-A3	Burchell et al., 1983
Breast	NS	FO23C5	Riva et al., 1988

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Colorectal	TAG-72 High M_r mucin	B72-3	Colcher et al., 1987
Colorectal	GP37	(17-1A) 1038-17-1A	Paul et al., 1986
Colorectal	Surface GP	CO17-1A	LoBuglio et al., 1988
Colorectal	CEA	ZCE-025	Patt et al., 1988
Colorectal	CEA	AB2	Griffin et al., 1988a
Colorectal	Cell surface AG	HT-29-15	Cohn et al., 1987
Colorectal	Secretory epithelium	250-30.6	Leydem et al., 1986
Colorectal	Surface glycoprotein	44X14	Gallagher et al., 1986
Colorectal	NS	A7	Takahashi et al., 1988
Colorectal	NS	GA73-3	Munz et al., 1986
Colorectal	NS	791T/36	Farrans et al., 1982
Colorectal	Cell Membrane & Cytoplasmatic Ag	28A32	Smith et al., 1987
Colorectal	CEA & Vindesin	28.19.8	Corvalen, 1987
Colorectal	gp72	X MMCO-791	Byers et al., 1987
Colorectal	high M_r mucin	DU-PAN-2	Lan et al., 1985
Colorectal	high M_r mucin	ID_3	Gangopadhyay et al., 1985
Colorectal	CEA 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Colorectal	60 Kd GP	$2C_8/2F_7$	Bhattacharya et al., 1985

Tumor	**Antigen Identity/ Characteristics**	**Monoclonal Antibodies**	**References**
Colorectal	CA-19-9 (or GICA)	CA-19-9 (1116NS 19-9)	Atkinson et al., 1982
Colorectal	Lewis a	PR5C5	Imperial Cancer Research Technology Mab Listing
Colorectal	Lewis a	PR4D2	Imperial Cancer Research Technology Mab Listing
Colorectal	Colon mucus	PR4D1	Imperial Cancer Research Technology Mab Listing
Melanoma	P97[a]	4-1	Woodbury et al., 1980
Melanoma	P97[a]	8-2 M_{17}	Brown, et al., 1981a
Melanoma	P97[b]	96-5	Brown, et al., 1981a
Melanoma	P97[c]	118-1, 133-2, (113-2)	Brown, et al., 1981a
Melanoma	P97[c]	L_1, L_{10}, R_{10} (R_{19})	Brown et al., 1981b
Melanoma	P97[d]	I_{12}	Brown et al., 1981b
Melanoma	P97[e]	K_5	Brown et al., 1981b
Melanoma	P155	6-1	Loop et al., 1981

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Melanoma	G_{D3} disialogan-gliosides	R24	Dippold et al., 1980
Melanoma	P210, p60, p250	5-1	Loop et al., 1981
Melanoma	P280 p440	225.28S	Wilson et al., 1981
Melanoma	GP 94, 75, 70 & 25	465.12S	Wilson et al., 1981
Melanoma	P240-P250, P450	9-2-27	Reisfeld et al., 1982
Melanoma	100, 77, 75 Kd	F11	Chee et al., 1982
Melanoma	94 Kd	376.96S	Imai et al., 1982
Melanoma	4 GP Chains	465.12S	Imai et al., 1982; Wilson et al., 1981
Melanoma	GP 74	15-75	Johnson & Reithmuller, 1982
Melanoma	GP 49	15-95	Johnson & Reithmuller, 1982
Melanoma	230 Kd	Mel-14	Carrel et al., 1982
Melanoma	92 Kd	Mel-12	Carrel et al., 1982
Melanoma	70 Kd	Me3-TB7	Carrel et al., 1:387, 1982
Melanoma	HMW MAA similar to 9-2-27 AG	225.28SD	Kantor et al., 1982
Melanoma	HMW MAA similar to 9-2-27 AG	763.24TS	Kantor et al., 1982

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Melanoma	GP95 similar to 376-96S 465-12S	705F6	Stuhlmiller et al., 1982
Melanoma	GP125	436910	Saxton et al., 1982
Melanoma	CD41	M148	Imperial Cancer Research Technology Mab listing
Gastrointestinal (GI)	high M_r mucin	ID3	Gangopadhyay et al., 1985
Gallbladder, Pancreas, Stomach	high M_r mucin	DU-PAN-2	Lan et al., 1985
Pancreas	NS	OV-TL3	Poels et al., 1984
Pancreas, Stomach, Esophagus	'TAG-72' high M_r mucin	B72-3	Thor et al., 1986
Stomach	'CEA' 180 Kd GP	CEA 11-H5	Wagener et al., 1984
Pancreas	HMFG-2 > 400 Kd GP	3-14-A3	Burchell et al., 1983
GI	NS	C COLI	Lemkin et al., 1984
Pancreas, Stomach	CA 19-9 (or GICA)	CA-19-9 (1116NS 19-9) and CA50	Szymendera, 1986
Pancreas	CA125 GP	OC125	Szymendera, 1986

Tumor	**Antigen Identity/ Characteristics**	**Monoclonal Antibodies**	**References**
Lung	$p185^{HER2}$	4D5, 3H4, 7C2, 6E9, 2C4, 7F3, 2H11, 3E8, 5B8, 7D3, SB8	Shepard et al., 1991
Non-small-cell lung cancer (NSCLC)			
NSCLC	high M_r mucin/glycolipid	MO v2	Miotti et al., 1985
NSCLC	'TAG -72' high M_r mucin	B72-3	Thor et al., 1986
NSCLC	High M_r mucin	DU-PAN-2	Lan et al., 1985
NSCLC	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984
Malignant Glioma	Cytoplastic antigen that consists of 85HG-22 cells	MUG 8-22	Stavrou, 1990
Malignant Glioma	Cell surface Ag that consists of 85HG-\63 cells	MUC 2-63	Stavrou, 1990
Malignant Glioma	Cell surface Ag that consists of 86HG-39 cells	MUC 2-39	Stavrou, 1990
Malignant Glioma	Cell surface Ag that consists of 86HG-39 cells	MUG 7-39	Stavrou, 1990

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
GI, Other	P53	PAb 240, PAb 246, PAb 1801	Imperial Cancer Research Technology MaB Listing
Small, Round-Cell Tumors	Neural cell adhesion molecules	ERIC-1	Imperial Cancer Research Technology MaB Listing
Medulloblas-tomas, Neuro-blastomas, Rhabdomyo-sarcomas		M148	Imperial Cancer Research Technology MaB Listing
Neuro-blastomas		FMH25	Imperial Cancer Research Technology MaB Listing
Kidneys & Glioblastomas	P155	6-1	Loop et al., 1981
Bladders & Laryngeal Tumors	"Ca Antigen" 350-390 kD	CA1	Ashall et al., 1982
Neuroblastoma	GD2	3F8	Cheung et al., 1986
Prostate	Gp48 48 kD GP	$4F_7/7A_{10}$	Bhattacharya et al., 1984
Prostate	60 kD GP	$2C_8/2F_7$	Bhattacharya et al., 1985

Tumor	Antigen Identity/ Characteristics	Monoclonal Antibodies	References
Thyroid	'CEA' 180 kD GP	CEA 11-H5	Wagener et al., 1984

As especially preferred recognition units for treating hematological tumors, antibodies or antibody fragments, such as CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21, CD5, CD37 and CD30, can also be mentioned.

As especially preferred recognition units for anti-angiogenic therapy, antibodies or fragments thereof, such as VCAM, CD31, ELAM, endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), phosphatidylserine, PSMA, VEGFR/VEGF complex or ED-B-fibronectin, can be mentioned.

The compounds that are mentioned below are especially preferred according to the invention as effector building blocks:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione,

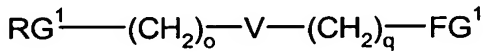
(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione.

In a compound of general formula (I) according to the invention that contains one of the above-mentioned building blocks, the hydrogen atoms in the above-mentioned building blocks are replaced in the positions indicated in formula (I) by radicals L^1-L^3, whereby radicals L^1-L^3 have the above-indicated meanings.

The invention also relates to linkers of general formula III^1

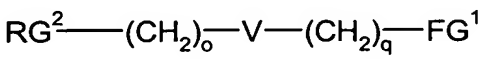


III¹,

in which

RG^1 can be an O=C=N group or an S=C=N group, and o, V, q and FG^1 have the meanings that are already mentioned above,

as well as linkers of general formula III^2

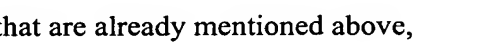


III²,

in which

RG^2 can be a Hal-C(=T)-CHR^{22} group or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group; R^{26} can be C_1-C_{10} alkyl, aryl, or aralkyl, and o, V, q, T and FG^1 have the meanings that are already mentioned above,

as well as linkers of general formula III^3



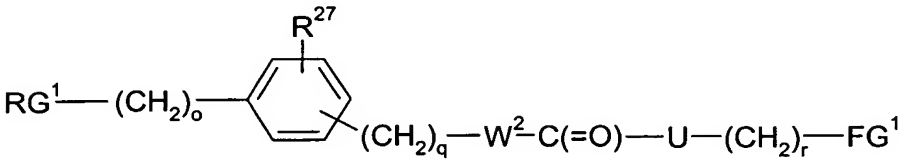
III³,

in which

RG^3 can be an OH group or an NHR^{24a} group or a COOH group, and o, V, q and FG^1 have the meanings that are already mentioned above;

but with the condition that the compound 1-(4-amino-phenyl)-pyrrole-2,5-dione is not included.

The invention also relates to linkers of general formula (IV^1):



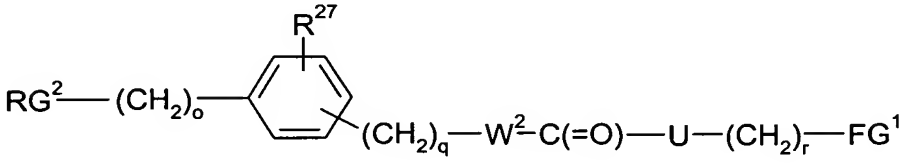
IV¹

,

in which

RG^1 is an O=C=N group or an S=C=N group, and o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linkers of general formula (IV^2):



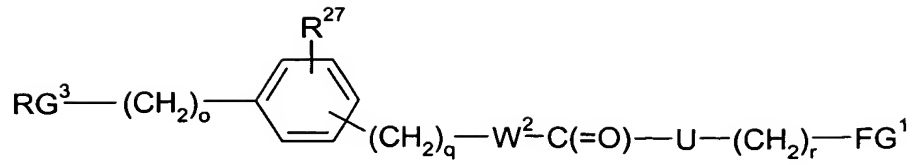
IV²

,

in which

RG^2 is a Hal-C(=T)-CHR^{22} group or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, whereby R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and R^{22}, R^{23}, T, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linkers of general formula (IV^3):



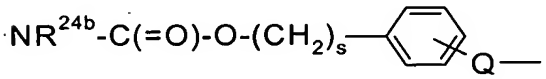
IV^3 ,

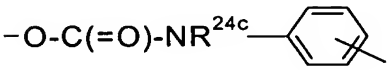
in which

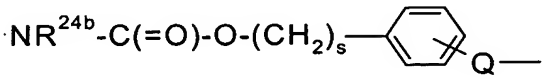
RG^3 is an OH group or an NHR^{24a} group or a COOH group, and R^{24a}, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1.

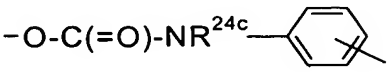
According to the invention, linkers of general formulas III^1, III^2 or III^3 are preferred, whereby V represents a bond or an aryl radical, o is equal to zero, and T is an oxygen atom.

In addition, linkers of general formulas III^1, III^2 or III^3 according to the invention are preferred, in which V represents a bond or an aryl radical or a group

 ; Q represents a bond or a group

 ; and o is 0 to 4. Especially preferred from the above are those linkers in which V represents a bond or a group

 ; Q represents a bond or a group

 ; o is equal to 0, 2 or 3; s is equal to 1; and T is an oxygen atom.

In addition, preferred according to the invention are linkers of general formulas IV^1, IV^2 or IV^3, in which o is zero to four and q is zero to three. Especially preferred from the above are those linkers in which o is 0, 2 or 3; W^1 is an oxygen atom; q is equal to 0; R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl; R^{23} is hydrogen or C_1-C_3 alkyl; R^{24a} is

hydrogen or C_1-C_3 alkyl; R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28}; R^{28} is hydrogen or C_1-C_5 alkyl; and U is oxygen, CHR^{22} or CHR^{22}-NR^{23}-C(=O).

The invention also relates to processes

to react a linker of general formula III^1 or IV^1 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and in which L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction optionally are protected,

to react a linker of general formula III^2 or IV^2 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a hydrogen atom, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected, or

to react a linker of general formula III^3 or IV^3 with a compound of general formula I, in which the condition that at least one group L^1, L^2 or L^4 represent a linker need not be met, and L^1 and/or L^2 and/or L^4 have the meaning of a C(=O)Hal group or a C(=S)Hal group, and free hydroxyl groups and/or amino groups that are not required for the reaction are optionally protected.

The invention also relates to the use of a compound of general formula I, whereby the substituents have the above-mentioned meanings, but the condition that at least one substituent L^1, L^2 or L^4 represents a linker of general formula III or IV need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl , in a process as described above.

The invention also relates to the use of a compound of general formula I, whereby the substituents have the above-mentioned meanings, but the condition that at least one

substituent L^1, L^2 or L^4 represent a linker of general formula III or IV need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(S)Cl, for the production of an effector recognition unit conjugate as described above.

The invention also relates to the use of a linker of general formula III^1, III^2, III^3, IV^1, IV^2 or IV^3 for the production of an effector conjugate, as described above.

The invention also relates to the use of a linker of general formula III^1, III^2, III^3, IV^1, IV^2 or IV^3 for the production of an effector recognition unit conjugate as described above.

The invention also relates to the use of a recognition unit, as described above, in a process according to the invention for the production of an effector recognition unit conjugate, as described above.

The invention also relates to the effector recognition unit conjugates according to the invention for use as medications or for the production of a medication or a pharmaceutical composition.

The invention finally relates to the use of the effector recognition unit conjugates according to the invention for the production of medications for the treatment of diseases that are linked with proliferative processes, such as tumors, inflammatory and/or neurodegenerative diseases, multiple sclerosis, Alzheimer's disease, or for the treatment of angiogenesis-associated diseases, such as tumor growth, rheumatoid arthritis or diseases of the ocular fundus.

Examples of the Synthesis of Linkers (L)

Example L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid

Example L1a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-propanoic acid ethyl ester

The solution of 15 g (89.5 mmol) of N-methylalanine ethyl ester-hydrochloride in 850 ml of anhydrous tetrahydrofuran is mixed at 23°C with 4.1 g of an approximately 60% sodium hydride dispersion and, after 3 hours, with 23.5 g of 3-acetylsulfanyl-propanoic acid chloride. It is allowed to react for two days, mixed with saturated sodium bicarbonate solution, and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 17.6 g (67.3 mmol, 75%) of the title compound is isolated as a colorless oil.

Example L1b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propanoic acid

The solution of 17.6 g (67.3 mmol) of the compound, presented according to Example LI, in 150 ml of methanol is mixed at 23°C with 44 ml of a 5M sodium hydroxide solution, and it is stirred for 5 hours. By adding 4N hydrochloric acid, a pH of 2 is set, and it is extracted with dichloromethane. The combined organic extracts are washed with saturated sodium chloride solution and dried on sodium sulfate. The residue

that is obtained after filtration and removal of the solvent (13.0 g, maximum 67.3 mmol) is further reacted without purification.

Example L1c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-propanoic acid methyl ester

The solution of 4.53 g (maximum 23.7 mol) of the crude product, presented according to Example L1b, in 135 ml of diethyl ether is esterified at 0°C with an ethereal solution of diazomethane. After removal of the solvent, 4.59 g (22.4 mmol, 94%) of the title compound is isolated as a pale yellow oil, which is further reacted without purification.

Example L1d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid methyl ester

The solution of 14 g (68.2 mmol) of the compound, presented according to Example L1c, in 180 ml of trichloromethane is added to the solution of 21 g of 2-methyldisulfanyl-isoindole-1,3-dione in 420 ml of trichloromethane, and it is stirred for 16 hours at 23°C. It is concentrated by evaporation, taken up in dichloromethane, and stirred for 0.5 hour. Solid is filtered off, the filtrate is concentrated by evaporation, and the residue is purified by chromatography on fine silica gel. 16.2 g (57.2 mmol, 84%) of the title compound is isolated as a colorless oil.

Example L1

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-propanoic acid

The solution of 10 g (35.3 mmol) of the compound, presented according to Example L1d, in 20 ml of ethanol is mixed with 1 l of phosphate puffer with a pH of 7,

pig liver esterase, and it is incubated at 27°C for 46 hours. By adding a 4N hydrochloric acid, the pH is adjusted to 1, it is extracted with dichloromethane, dried on sodium sulfate, and after filtration and removal of the solvent, 8.3 g (30.8 mmol, 87%) of the title compound is isolated as a colorless oil, which is reacted without further purification.

^{1}H-NMR ($CDCl_3$): δ = 1.43+1.51 (3H), 2.55+2.63 (3H), 2.87 (2H), 2.88+3.00 (3H), 3.08-3.26 (2H), 4.63+5.19 (1H), 7.90 (1H) ppm.

Example L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid

Example L2a

2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-acetic acid ethyl ester

7.13 g (46.4 mmol) of N-methylglycine ethyl ester-hydrochloride is reacted analogously to Example L1a, and 6.9 g (27.9 mmol, 60%) of the title compound is isolated as a colorless oil.

Example L2b

[(3-Mercapto-propionyl)-methyl-amino]-acetic acid

7.6 g (30.7 mmol) of the compound that is presented according to Example L2a is reacted analogously to Example L1b, and 4.92 g (27.8 mmol, 90%) of the title compound is isolated as a colorless oil.

Example L2c

[(3-Mercapto-propionyl)-methyl-amino]-acetic acid methyl ester

4.92 g (27.8 mmol) of the compound that is presented according to Example L2b is reacted analogously to Example L1c, and 5.01 g (26.2 mmol, 94%) of the title compound is isolated as a colorless oil.

Example L2d

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid methyl ester

2.00 g (10.5 mmol) of the compound that is presented according to Example L2c is reacted analogously to Example L1d, and 2.33 g (8.65 mmol, 82%) of the title compound is isolated as a colorless oil.

Example L2

[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-acetic acid

2.00 g (7.83 mmol) of the compound that is presented according to Example L2d is reacted analogously to Example L1, and 0.64 g (2.51 mmol, 32%) of the title compound is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 2.41+2.56 (3H), 2.61-3.27 (7H), 3.98 (2H), 4.38 (1H) ppm.

Example L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propionic acid

Example L3a

(S) 2-[(3-Acetylsulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid ethyl ester

7.73 g (31.7 mmol) of N-methylphenylalanine ethyl ester-hydrochloride is reacted analogously to Example L1a, and 2.3 g (6.82 mmol, 22%) of the title compound is isolated as a colorless oil.

Example L3b

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propanoic acid

1.09 g (3.23 mmol) of the compound that is presented according to Example L3a is reacted analogously to Example L1b, and 0.744 g (2.78 mmol, 86%) of the title compound is isolated as a colorless oil.

Example L3c

(S) 2-[(3-Mercapto-propionyl)-methyl-amino]-3-phenyl-propanoic acid methyl ester

0.74 g (2.77 mmol) of the compound that is presented according to Example L3b is reacted analogously to Example L1c, and 0.77 g (2.74 mmol, 99%) of the title compound is isolated as a colorless oil.

Example L3d

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid methyl ester

0.77 g (2.74 mmol) of the compound that is presented according to Example L3c is reacted analogously to Example L1d, and 0.72 g (2.00 mmol, 73%) of the title compound is isolated as a colorless oil.

Example L3

(S) 2-[(3-Methyltrisulfanyl-propionyl)-methyl-amino]-3-phenyl-propanoic acid

0.72 g (2.00 mmol) of the compound that is presented according to Example L3d is reacted analogously to Example L1, and 0.49 g (1.42 mmol, 71%) of the title compound is isolated as a colorless oil.

Example L4

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid

20.0 g (193.9 mmol) of 4-aminobutyric acid is mixed with 19 g of maleic acid anhydride, 290 ml of acetic acid, and it is heated for 4 hours in an oil bath at 130°C. It is azeotropically concentrated by evaporation with repeated addtiion of toluene, the residue is taken up in dichloromethane and purified by chromatography on fine silica gel. 17.1 g (93.4 mmol, 48%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.93 (2H), 2.38 (2H), 3.60 (2H), 6.71 (2H) ppm.

Example L4a

1-(3-Isocyanato-propyl)-pyrrole-2,5-dione

5.0 g (27.3 mmol) of the compound that is presented according to Example L4 is dissolved in 90 ml of tetrahydrofuran, mixed with 8 ml of triethylamine and 6.17 ml of phosphoric acid diphenylester azide, and it is stirred for 1.5 hours at 23°C. Then, it is mixed with 110 ml of toluene, the tetrahydrofuran is distilled off, and it is heated for 2 hours to 70°C. The crude product is purified by chromatography on fine silica gel. 1.77 g (9.82 mmol, 36%) of the title compound is isolated.

Example L5

6-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid

100 g (762 mmol) of 6-aminocaproic acid is reacted analogously to Example L5, and 93.8 g (444 mmol, 58%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.34 (2H), 1.55-1.70 (4H), 2.34 (2H), 3.51 (2H), 6.69 (2H) ppm.

Example L5a

1-(5-Isocyanato-pentyl)-pyrrole-2,5-dione

10.0 g (47.3 mmol) of the compound that is presented according to Example L5 is reacted analogously to Example L4a, and 3.19 g (15.3 mmol, 32%) of the title compound is isolated as a colorless oil.

Example L6

11-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid

10 g (49.7 mmol) of 11-aminoundecanoic acid is reacted analogously to Example L5, and 6.29 g (22.4 mmol, 45%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR ($CDCl_3$): δ = 1.19-1.36 (12H), 1.51-1.67 (4H), 2.34 (2H), 3.49 (2H), 6.68 (2H) ppm.

Example L6a

1-(10-Isocyanato-decyl)-pyrrole-2,5-dione

5.28 g (18.8 mmol) of the compound that is presented according to Example L6 is reacted analogously to Example L4a, and 3.37 g (12.1 mmol, 64%) of the title compound is isolated as a colorless oil.

Example L7

1-(4-Amino-phenyl)-pyrrole-2,5-dione

The solution of 21.6 g (200 mmol) of 1,4-phenylenediamine in 200 ml of tetrahydrofuran is mixed over 1.5 hours with the solution of 19.6 g of maleic acid anhydride, and it is stirred for 22 hours at 23°C. It is filtered, rewashed with tetrahydrofuran, and the filtrate is dried. 37.1 g (197 mmol, 98%) of the title compound is isolated as a crystalline solid.

^{1}H-NMR (d6-DMSO): δ = 6.28 (1H), 6.48 (1H), 6.53 (2H), 7.30 (2H), 7.50-9.00 (2H) ppm.

Example L8

1-(4-Hydroxy-phenyl)-pyrrole-2,5-dione

The suspension that consists of 5.0 g (45.8 mmol) of 4-aminophenol, 4.49 g of maleic acid anhydride and 40 ml of acetic acid is refluxed for 3 hours. It is concentrated by evaporation, residual acetic acid is removed azeotropically by repeated distillation with acetic acid, and the residue is purified by chromatography on fine silica gel. 2.83 g (15.0 mmol, 33%) of the title compound is isolated.

^{1}H-NMR (d6-DMSO): δ = 6.83 (2H), 7.09 (2H), 7.13 (2H), 9.71 (1H) ppm.

Example L9

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

The solution of 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol in 250 ml of dichloromethane is mixed with 6.1 g of N,N'-dicyclohexylcarbodiimide and 2.4 ml of

pyridine, and the solution of 5.5 g of the compound, presented according to Example L4, in 250 ml of dichloromethane, is added in drops within 15 minutes. It is stirred for one more hour at 23°C, filtered, the filtrate is concentrated by evaporation and purified by chromatography on fine silica gel. 1.73 g (5.2 mmol, 18%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 2.07 (3H), 2.67 (2H), 3.67 (2H), 4.79 (2H), 6.72 (2H), 7.28 (1H), 7.66 (1H), 8.10 (1H) ppm.

Example L10

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol is reacted with 6.34 g of the compound that is presented according to Example L5, and after working-up and purification, 3.78 g (10.4 mmol, 35%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.42 (2H), 1.66 (2H), 1.88 (2H), 2.64 (2H), 3.55 (2H), 4.78 (2H), 6.69 (2H), 7.21 (1H), 7.64 (1H), 8.09 (1H) ppm.

Example L11

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-hydroxymethyl-2-nitro-phenyl ester

Analogously to Example L9, 5.0 g (29.6 mmol) of 4-hydroxymethyl-2-nitro-phenol is reacted with 8.44 g of the compound that is presented according to Example L6, and after working-up and purification, 3.78 g (10.4 mmol, 35%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.21-1.63 (14H), 1.76 (2H), 1.99 (1H), 2.63 (2H), 3.51 (2H), 4.78 (2H), 6.68 (2H), 7.21 (1H), 7.65 (1H), 8.10 (1H) ppm.

Examples of the Synthesis of Effector-Linker Conjugates (EL)

Example EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL1a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 6.0 g (7.93 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process that is described in WO 00/66589, in 186 ml of anhydrous dichloromethane is mixed at 0°C with 26.4 ml of a 20% solution of trifluoroacetic acid in dichloromethane, and it is stirred for 6 hours at 0°C. It is poured into saturated sodium bicarbonate solution, extracted with dichloromethane, the combined organic extracts are washed with water and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 3.32 g (5.17 mmol, 65%) of the title compound is isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = 0.09 (3H), 0.12 (3H), 0.93 (9H), 1.00 (3H), 1.06 (3H), 1.22 (3H), 1.70 (3H), 1.03-1.77 (5H), 1.95 (1H), 2.31-2.56 (6H), 2.83 (3H), 2.87 (1H), 3.00 (1H), 3.30 (1H), 3.90 (1H), 4.09 (1H), 4.94-5.03 (2H), 5.20 (1H), 5.77 (1H), 5.88 (1H), 7.34 (1H), 7.78 (1H), 7.95 (1H) ppm.

Example EL1b

(4S,7R,8S,9S,13Z,16S)-3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is presented according to Example EL1a is dissolved in a mixture that consists of 1.5 ml of trichloromethane and 1.5 ml of dimethylformamide, mixed with 144 mg of the linker that is presented according to Example L4a, 79 mg of copper(I) chloride, and it is heated for 18 hours to 70°C. The crude mixture is purified by chromatography on thin-layer plates, and 51 mg (62 µmol, 80%) of the title compound is isolated as a colorless oil.

Example EL1

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

The solution of 41 mg (50 µmol) of the compound, presented according to Example 1b, in a mixture that consists of 0.8 ml of tetrahydrofuran and 0.8 ml of acetonitrile is mixed with 310 µl of hexafluorosilicic acid, 310 µl of hydrogen fluoride-pyridine complex, and it is stirred for 23 hours at 23°C. It is poured into a 5% sodium hydroxide solution, extracted with ethyl acetate, the combined organic extracts are washed with a saturated sodium chloride solution and dried on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on thin-layer plates, and 26 mg (36.7 µmol, 73%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.99 (3H), 1.14 (3H), 1.17 (3H), 1.20-1.51 (3H), 1.54-1.87 (6H), 1.70 (3H), 2.22 (1H), 2.28-3.02 (9H), 2.83 (3H), 3.31 (1H), 3.45 (1H), 3.68 (1H), 4.44+4.83 (1H), 4.99 (1H), 5.03 (1H), 5.15 (1H), 5.61 (1H), 5.72 (1H), 5.91 (1H), 6.68 (2H), 7.36 (1H), 7.78 (1H), 7.90 (1H) ppm.

Example EL2

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and

(1R,3S,7S,10R,11S,12S,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

The solution of 44 mg (62.2 µmol) of the compound, presented according to Example 1, in 2.0 ml of dichloromethane is cooled to -50°C and mixed in portions over a period of 1.5 hours with a total of 1.7 ml of an approximately 0.1 M solution of dimethyl dioxiram in acetone. It is poured into a saturated sodium thiosulfate solution, extracted with dichloromethane, and the combined organic extracts are dried on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on thin-layer plates, and 22.7 mg (31.4 µmol, 50%) of title compound A as well as 7.6 mg (10.5 µmol, 17%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.01 (3H), 1.14 (3H), 1.16 (3H), 1.20-1.94 (8H), 1.32 (3H), 2.11-2.74 (9H), 2.82 (1H), 2.84 (3H), 3.30 (2H), 3.48 (2H), 3.68 (1H), 4.36+4.93 (1H), 4.99 (1H), 5.04 (1H), 5.54 (1H), 5.69 (1H), 6.05 (1H), 6.68 (2H), 7.32 (1H), 7.80 (1H), 7.88 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 1.02 (6H), 1.26 (3H), 1.33 (1H), 1.23-2.27 (12H), 2.54-2.78 (4H), 2.82 (3H), 2.91 (1H), 3.13 (1H), 3.40 (2H), 3.66 (1H), 4.11 (1H), 4.84 (1H), 4.95 (1H), 5.01 (1H), 5.70 (1H), 5.81+5.93 (1H), 6.04+6.13 (1H), 6.69 (2H), 7.35 (1H), 7.75 (1H), 7.90+7.99 (1H) ppm.

Example EL3

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL3a

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is presented according to Example EL1a is reacted analogously to Example EL1b with the linker that is produced according to Example L5a, and after purification, 39 mg (45.9 µmol, 59%) of the title compound is isolated as a colorless oil.

Example EL3

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

84 mg (98.8 μmol) of the compound that is presented according to Example EL3a is reacted analogously to Example EL1, and after purification, 43 mg (58.4 μmol, 59%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.89 (3H), 0.96 (3H), 0.85-1.97 (17H), 1.12 (3H), 2.16-3.01 (10H), 2.82 (3H), 3.44 (1H), 3.65 (1H), 4.41+4.53 (1H), 4.98 (1H), 5.03 (1H), 5.15 (1H), 5.60 (1H), 5.71 (1H), 5.90 (1H), 6.68 (2H), 7.35 (1H), 7.77 (1H), 7.89+7.96 (1H) ppm.

Example EL4

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and

(1R,3S,7S,10R,11S,12S,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

26 mg (35.3 μmol) of the compound that is presented according to Example EL3 is reacted analogously to Example EL2, and after purification, 9.1 mg (12.1 μmol, 34%) of title compound A as well as 3.0 mg (4.0 μmol, 11%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.83-1.94 (15H), 0.98 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 2.15-2.82 (8H), 2.84 (3H), 3.44 (2H), 3.51 (1H), 3.66 (1H), 4.46 (1H), 4.99

(1H), 5.04 (1H), 5.54 (1H), 5.69 (1H), 6.06 (1H), 6.68 (2H), 7.33 (1H), 7.80 (1H), 7.89 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.78-2.74 (23H), 1.01 (3H), 1.03 (3H), 1.33 (3H), 2.82 (3H), 2.91 (1H), 3.14 (1H), 3.39 (1H), 3.47 (2H), 3.67 (1H), 4.12 (1H), 4.49 (1H), 4.92-5.06 (2H), 5.53+5.80 (1H), 5.69 (1H), 6.11 (1H), 6.68 (2H), 7.34 (1H), 7.74+7.79 (1H), 7.89+8.02 (1H) ppm.

Example EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

Example EL5a

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

50 mg (78 µmol) of the compound that is presented according to Example EL1a is reacted analogously to Example EL1b with the linker that is produced according to Example L6a, and after purification, 56 mg (60.8 µmol, 78%) of the title compound is isolated as a colorless oil.

Example EL5

(4S,7R,8S,9S,13Z,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

20 mg (21.7 µmol) of the compound that is presented according to Example EL5a is reacted analogously to Example EL1, and after purification, 10 mg (12.4 µmol, 57%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.91-1.87 (22H), 0.97 (3H), 1.13 (3H), 1.17 (3H), 1.70 (3H), 2.18-2.69 (8H), 2.80 (1H), 2.82 (3H), 2.96 (1H), 3.47 (1H), 3.50 (2H), 3.66 (1H), 3.97+4.36 (1H), 4.98 (1H), 5.04 (1H), 5.16 (1H), 5.61 (1H), 5.72 (1H), 5.91 (1H), 6.68 (2H), 7.37 (1H), 7.77 (1H), 7.90+7.97 (1H) ppm.

Example EL6

(1S,3S,7S,10R,11S,12S,16R)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (A) and

(1R,3S,7S,10R,11S,12S,16S)-[10-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester (B)

18 mg (22 µmol) of the compound that is presented according to Example EL5 is reacted analogously to Example EL2, and after purification, 9.2 mg (11.2 µmol, 51%) of title compound A as well as 3.2 mg (3.9 µmol, 18%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 1.03-1.67 (21H), 1.71-1.94 (3H), 2.18-2.78 (9H), 2.83 (3H), 3.50 (3H), 3.66 (1H), 3.87+4.43 (1H),

4.98 (1H), 5.04 (1H), 5.53 (1H), 5.69 (1H), 6.07 (1H), 6.68 (2H), 7.33 (1H), 7.80 (1H), 7.89+7.93 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.80-1.64 (21H), 1.01 (3H), 1.03 (3H), 1.25 (3H), 1.33 (3H), 1.79-2.25 (5H), 2.34+3.14 (1H), 2.52-2.76 (4H), 2.81 (3H), 2.91 (1H), 3.40 (1H), 3.51 (2H), 3.67+3.82 (1H), 4.13+4.26 (1H), 4.46 (1H), 4.94 (1H), 5.01 (1H), 5.70 (1H), 5.81+5.94 (1H), 6.05+6.12 (1H), 6.68 (2H), 7.36 (1H), 7.74 (1H), 7.91+8.02 (1H) ppm.

Example EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Example EL7a

(4S,7R,8S,9S,13Z,16S)-7-Allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione

The solution of 5.3 g (7.01 mmol) of (4S,7R,8S,9S,13Z,16S)-7-allyl-4,8-bis(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione, which was produced analogously to the process described in WO 00/66589, in a mixture that consists of 85 ml of tetrahydrofuran and 85 ml of acetonitrile, is mixed with 31.7 ml of hexafluorosilicic acid, cooled to 0°C, 8.1 ml of trifluoroacetic acid is added in drops, and it is stirred for 20 hours at 0°C. It is poured into water, neutralized by adding a saturated sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic extracts are washed with saturated sodium chloride solution, dried on sodium sulfate, and the residue that is

obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 2.82 g (4.39 mmol, 63%) of the title compound is isolated as a colorless solid.

^{1}H-NMR ($CDCl_3$): δ = -0.09 (3H), 0.08 (3H), 0.84 (9H), 1.08 (3H), 1.10 (3H), 1.12 (3H), 1.21-1.86 (5H), 1.70 (3H), 2.15 (1H), 2.29-2.97 (8H), 2.84 (3H), 3.14 (1H), 3.96 (1H), 4.03 (1H), 4.97-5.06 (2H), 5.23 (1H), 5.61 (1H), 5.77 (1H), 7.35 (1H), 7.79 (1H), 7.93 (1H) ppm.

Example EL7b

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) of the compound that is presented according to Example EL7a is reacted analogously to Example EL1b with the linker that is produced according to Example L4a, and after purification, 121 mg (147 µmol, 94%) of the title compound is isolated as a colorless oil.

Example EL7

(4S,7R,8S,9S,13Z,16S)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

46 mg (56 µmol) of the compound that is presented according to Example EL7b is reacted analogously to Example EL1, and after purification, 17 mg (24 µmol, 43%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.99-1.30 (2H), 1.03 (3H), 1.07 (3H), 1.21 (3H), 1.51-1.97 (6H), 1.72 (3H), 2.27-2.61 (6H), 2.83 (3H), 2.88 (1H), 3.09 (1H), 3.14 (2H), 3.51 (1H),

3.58 (2H), 4.04 (1H), 4.96-5.04 (2H), 5.12 (1H), 5.19 (1H), 5.28 (1H), 5.75 (1H), 5.86 (1H), 6.66 (2H), 7.35 (1H), 7.78 (1H), 7.96 (1H) ppm.

Example EL8

(1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) and (1S,3S,7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]-heptadec-11-yl ester (B)

29 mg (41 μmol) of the compound that is presented according to Example EL7 is reacted analogously to Example EL2, and after purification, 18 mg (24.9 μmol, 61%) of title compound A as well as 3.0 mg (4.1 μmol, 10%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.05 (3H), 1.24 (3H), 1.26 (3H), 1.12-1.83 (9H), 2.12-2.46 (4H), 2.59 (2H), 2.76 (1H), 2.84 (3H), 3.14 (2H), 3.59 (3H), 3.98 (1H), 4.10 (1H), 4.95-5.02 (2H), 5.17 (2H), 5.77 (1H), 6.19 (1H), 6.70 (2H), 7.38 (1H), 7.82 (1H), 7.97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.96 (3H), 1.01 (3H), 1.13-1.86 (11H), 1.28 (3H), 1.32 (1H), 2.16-2.50 (6H), 2.84 (3H), 3.02 (1H), 3.15 (2H), 3.50 (1H), 3.61 (2H), 3.88 (1H), 4.19 (1H), 4.96-5.04 (2H), 5.13 (1H), 5.28 (1H), 5.78 (1H), 6.33 (1H), 6.71 (2H), 7.36 (1H), 7.81 (1H), 7.96 (1H) ppm.

Example EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Example EL9a

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-*tert*-butyl-dimethylsilyloxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

100 mg (156 µmol) of the compound that is presented according to Example EL7a is reacted analogously to Example EL1b with the linker that is produced according to Example L5a, and after purification, (65.9 µmol, 42%) of the title compound is isolated as a colorless oil.

Example EL9

(4S,7R,8S,9S,13Z,16S)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

56 mg (65.9 µmol) of the compound that is presented according to Example EL7b is reacted analogously to Example EL1, and after purification, 24.7 mg (33.6 µmol, 51%) of the title compound is isolated as a colorless foam.

^{1}H-NMR ($CDCl_3$): δ = 0.97-1.84 (11H), 1.02 (3H), 1.07 (3H), 1.20 (3H), 1.71 (3H), 1.91 (1H), 2.27-2.57 (6H), 2.84 (3H), 2.88 (1H), 2.95 (1H), 3.16 (2H), 3.51 (3H), 4.02 (1H), 4.46+4.83 (1H), 4.94-5.03 (2H), 5.15 (1H), 5.20 (1H), 5.74 (1H), 5.84 (1H), 6.68 (2H), 7.35 (1H), 7.80 (1H), 7.96 (1H) ppm.

Example EL10

(1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (A) and (1S,3S,7S,10R,11S,12S,16R)-[5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester (B)

24.7 mg (33.6 µmol) of the compound that is presented according to Example EL9 is reacted analogously to Example EL2, and after purification, 16.7 mg (22.2 µmol, 66%) of title compound A as well as 2.0 mg (2.7 µmol, 8%) of title compound B are isolated in each case as a colorless foam.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.98 (3H), 1.04 (3H), 1.10-1.75 (13H), 1.23 (3H), 1.26 (3H), 2.09-2.62 (6H), 2.75 (1H), 2.84 (3H), 3.15 (2H), 3.51 (2H), 3.57 (1H), 3.99 (1H), 4.08 (1H), 4.46+4.74 (1H), 4.93-5.02 (2H), 5.18 (1H), 5.76 (1H), 6.18 (1H), 6.68 (2H), 7.38 (1H), 7.82 (1H), 7.97 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ = 0.83-1.85 (13H), 0.95 (3H), 1.01 (3H), 1.27 (3H), 1.32 (3H), 2.17-2.49 (6H), 2.84 (3H), 3.03 (1H), 3.17 (2H), 3.48 (1H), 3.53 (2H), 3.86 (1H), 4.18 (1H), 4.66 (1H), 4.94-5.03 (2H), 5.27 (1H), 5.76 (1H), 6.33 (1H), 6.69 (2H), 7.35 (1H), 7.81 (1H), 7.96 (1H) ppm.

Example EL11

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-carbamic acid 7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-

8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester

10 mg (19.7 μmol) of (1S,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadecane is reacted analogously to Example EL1b with the linker that is produced according to Example L4a, and after purification, 7 mg (8.06 μmol, 41%) of the title compound is isolated as a colorless oil.

^{1}H-NMR ($CDCl_3$): δ = 0.88-2.20 (13H), 1.03 (3H), 1.05 (3H), 1.10 (3H), 1.24 (3H), 1.28 (3H), 2.08 (3H), 2.63-2.85 (4H), 2.71 (3H), 2.99-3.25 (3H), 3.41-3.50 (3H), 3.62 (2H), 4.88-5.70 (5H), 6.52 (1H), 6.69 (2H), 6.71 (2H), 7.02 (1H) ppm.

Example EL12

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Example EL12a

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester

The solution of 1.0 g (1.56 mmol) of the compound, presented according to Example EL1a, in 20 ml of dichloromethane is mixed at 0°C with the solution of 285 mg of triphosgene in 6 ml of dichloromethane, 160 μl of pyridine, and it is stirred for 2.5 hours at 23°C. It is concentrated by evaporation, the residue is taken up in ethyl acetate,

washed with water and saturated sodium chloride solution, and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 1.08 g (1.53 mmol, 98%) of the title compound is isolated.

Example EL12b

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

The solution of 267 mg (370 μmol) of the compound, presented according to Example EL12a, in 16 ml of ethyl acetate, is mixed with 51 μl of triethylamine, 700 mg of the compound that is presented according to Example L8, and it is stirred for 16 hours at 23°C. It is poured into water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried on magnesium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 188 mg (219 μmol, 59%) of the title compound is isolated.

Example EL12

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL1, 248 mg (289 µmol) of the compound that is presented according to Example EL12a is reacted, and after working-up and purification, 149 mg (201 µmol, 69%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.08 (3H), 1.14 (3H), 1.26 (3H), 1.04-1.90 (8H), 2.24-2.57 (6H), 2.68-2.99 (3H), 2.81 (3H), 3.45 (1H), 3.72 (1H), 5.02 (1H), 5.06 (1H), 5.17 (1H), 5.65 (1H), 5.74 (1H), 5.98 (1H), 6.79 (2H), 6.88 (2H), 7.21 (2H), 7.33 (1H), 7.64 (1H), 7.97 (1H) ppm.

Example EL13

(1S,3S,7S,10R,11S,12S,16R)-Carboxylic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL2, 144 mg (194 µmol) of the compound that is presented according to Example EL12 is reacted, and after working-up and purification, 89 mg (117 µmol, 60%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.10 (3H), 1.14 (3H), 1.27 (3H), 1.32 (3H), 1.19-1.85 (7H), 2.08-2.89 (8H), 2.81 (3H), 3.50 (1H), 3.70 (1H), 5.02 (1H), 5.07 (1H), 5.58 (1H), 5.72 (1H), 6.10 (1H), 6.81 (2H), 6.88 (2H), 7.21 (2H), 7.31 (1H), 7.68 (1H), 7.93 (1H) ppm.

Example EL14

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Example EL14a

(4S,7R,8S,9S,13Z,16S)-Chloroformic acid-7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester

Analogously to Example EL12a, 1.0 g (1.56 mmol) of the compound that is presented according to Example EL7a is reacted, and 1.05 g (1.49 mmol, 96%) of the title compound is isolated.

Example EL14b

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

The solution of 313 mg (0.44 mmol) of the compound, presented according to Example EL14a, in 19 ml of ethyl acetate is mixed with 840 mg of the compound that is presented according to Example L8, 61.5 µl of triethylamine, and it is stirred for 16 hours at 23°C. It is mixed with water, extracted several times with ethyl acetate, the combined organic extracts are washed with saturated sodium chloride solution and dried on sodium sulfate. The residue that is obtained after filtration and removal of the solvent is purified by chromatography on fine silica gel. 298 mg (348 µmol, 79%) of the title compound is isolated.

Example EL14

(4S,7R,8S,9S,13Z,16S)-Carboxylic acid 7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL1, 304 mg (355 µmol) of the compound that is presented according to Example EL14a is reacted, and after working-up and purification, 67 mg (90 µmol, 25%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.09 (3H), 1.11 (3H), 0.84-2.02 (7H), 1.27 (3H), 1.72 (3H), 2.29-2.58 (6H), 2.84 (3H), 2.89 (1H), 2.96 (1H), 3.63 (1H), 4.03 (1H), 5.06 (2H), 5.23 (2H), 5.80 (1H), 5.85 (1H), 6.86 (2H), 7.30 (2H), 7.35 (1H), 7.39 (1H), 7.80 (1H), 7.96 (1H) ppm.

Example EL15

(1S,3S,7S,10R,11S,12S,16R)-Carboxylic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-phenyl ester

Analogously to Example EL2, 67 mg (90 µmol) of the compound that is presented according to Example EL14 is reacted, and after working-up and purification, 32 mg (42 µmol, 47%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.05 (3H), 1.06 (3H), 1.25 (3H), 1.35 (3H), 1.21-1.90 (7H), 2.18 (2H), 2.33-2.67 (4H), 2.73 (1H), 2.85 (3H), 3.79 (1H), 4.11 (1H), 4.33 (1H), 5.02 (1H), 5.07 (1H), 5.31 (1H), 5.81 (1H), 6.27 (1H), 6.86 (2H), 7.29 (2H), 7.35-7.41 (3H), 7.83 (1H), 7.99 (1H) ppm.

Example EL16

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-methyltrisulfanyl-*N*-methyl-propionamide

The solution of 7 mg (13 µmol) of (1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-penta-methyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione, which was produced analogously to the process described in WO 99/01124, in 0.5 ml of dichloromethane is mixed with 7 mg of the compound that is presented according to Example L1, 0.4 mg of 4-dimethylaminopyridine and 4 mg of N,N'-dicyclohexylcarbodiimide are added, and it is stirred for 20 minutes at 23°C. Precipitated urea is filtered out, and it is purified by chromatography on a preparative thin-layer plate. 5 mg (6.5 µmol, 50%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.00 (3H), 1.08 (3H), 1.17 (3H), 1.23-1.77 (5H), 1.28 (3H), 1.36 (3H), 1.39 (3H), 1.88-2.13 (3H), 2.10 (3H), 2.37 (1H), 2.49-2.66 (2H), 2.55 (3H), 2.77-2.92 (4H), 2.97 (3H), 3.16 (2H), 3.31 (1H), 3.77 (1H), 4.08 (1H), 4.19 (1H), 4.62 (1H), 4.76 (1H), 5.25 (1H), 5.45 (1H), 6.57 (1H), 7.01 (1H), 7.06 (1H) ppm.

Example EL17

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-methyltrisulfanyl-propionyl)-amino]-propionic acid-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

Analogously to Example EL16, 10 mg (19 µmol) of (1S,3S(E),7S,10R,11S, 12S,16R)-7,11-dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0] heptadecane-5,9-dione, which was

produced analogously to the process that is described in WO 99/01124, is reacted, and 2.2 mg (2.8 μmol, 15%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.09 (3H), 1.18 (3H), 1.27 (1H), 1.28 (3H), 1.32-1.76 (3H), 1.37 (3H), 1.47 (3H), 1.95 (1H), 2.06 (1H), 2.12 (3H), 2.38 (1H), 2.51-2.63 (2H), 2.56 (3H), 2.78-2.92 (5H), 2.97+3.01 (3H), 3.13-3.35 (3H), 3.71 (1H), 3.77 (1H), 4.00 (1H), 4.18 (1H), 5.25 (1H), 5.39 (2H), 5.45 (1H), 6.60 (1H), 7.17 (1H) ppm.

Example EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL18a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 200 mg (284 μmol) of the compound that is presented according to Example EL12a is reacted with 770 mg of the compound that is presented according to Example L9, and after working-up and purification, 129 mg (129 μmol, 45%) of the title compound is isolated.

Example EL18

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 129 mg (129 μmol) of the compound that is presented according to Example EL18a is reacted, and after working-up and purification, 71 mg (80 μmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.88-2.11 (11H), 1.02 (3H), 1.14 (3H), 1.71 (3H), 2.23-2.56 (6H), 2.63-2.71 (3H), 2.74 (3H), 2.97 (1H), 3.39 (1H), 3.68 (3H), 4.58 (1H), 4.78 (1H), 5.01 (1H), 5.05 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.73 (2H), 7.19 (1H), 7.31 (1H), 7.36 (1H), 7.75 (1H), 7.77 (1H), 7.95 (1H) ppm.

Example EL19

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 71 mg (80 μmol) of the compound that is presented according to Example EL18 is reacted, and after working-up and purification, 41 mg (45 μmol, 57%) of title compound A as well as 12 mg (13 μmol, 17%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.04 (3H), 1.14 (3H), 1.16 (3H), 1.32 (3H), 1.34-1.84 (6H), 2.01-2.74 (12H), 2.78 (3H), 2.86 (1H), 3.44 (1H), 3.68 (3H), 4.56 (1H), 4.74 (1H),

5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.07 (1H), 6.73 (2H), 7.20 (1H), 7.32 (1H), 7.36 (1H), 7.77 (1H), 7.81 (1H), 7.90 (1H) ppm.

Example EL20

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL20a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 243 mg (345 µmol) of the compound that is presented according to Example EL12a is reacted with 1 g of the compound that is presented according to Example L10, and after working-up and purification, 25 mg (24 µmol, 7%) of the title compound is isolated.

Example EL20

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 212 mg (206 µmol) of the compound that is presented according to Example EL20a is reacted, and after working-up and purification, 117 mg (128 µmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.01 (3H), 1.14 (6H), 1.04-2.78 (20H), 1.70 (3H), 2.74 (3H), 2.97 (1H), 3.39 (1H), 3.56 (2H), 3.68 (1H), 4.11 (1H), 4.58 (1H), 4.77 (1H), 5.00 (1H), 5.05 (1H), 5.18 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.69 (2H), 7.12 (1H), 7.29 (1H), 7.36 (1H), 7.75 (2H), 7.94 (1H) ppm.

Example EL21

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 117 mg (128 μmol) of the compound that is presented according to Example EL20 is reacted, and after working-up and purification, 63 mg (68 μmol, 53%) of title compound A as well as 19 mg (20 μmol, 16%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.03 (3H), 1.14 (3H), 1.15 (3H), 1.32 (3H), 1.07-2.75 (22H), 2.77 (3H), 2.86 (1H), 3.44 (1H), 3.55 (2H), 3.69 (1H), 4.55 (1H), 4.77 (1H), 5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.08 (1H), 6.70 (2H), 7.14 (1H), 7.31 (1H), 7.35 (1H), 7.76 (1H), 7.80 (1H), 7.90 (1H) ppm.

Example EL22

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL22a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 243 mg (345 μmol) of the compound that is presented according to Example EL12a is reacted with 1.19 g of the compound that is presented according to Example L11, and after working-up and purification, 171 mg (155 μmol, 45%) of the title compound is isolated.

Example EL22

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-8-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-4-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 171 mg (155 μmol) of the compound that is presented according to Example EL22a is reacted, and after working-up and purification, 108 mg (110 μmol, 71%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.14 (6H), 0.88-2.56 (28H), 1.70 (3H), 2.63 (2H), 2.71 (1H), 2.74 (3H), 2.98 (1H), 3.39 (1H), 3.50 (2H), 3.69 (1H), 4.58 (1H), 4.77 (1H), 5.00 (1H), 5.05 (1H), 5.17 (1H), 5.56 (1H), 5.71 (1H), 5.97 (1H), 6.68 (2H), 7.11 (1H), 7.29 (1H), 7.36 (1H), 7.75 (1H), 7.76 (1H), 7.94 (1H) ppm.

Example EL23

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-

4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S,12S, 16S)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 108 mg (110 µmol) of the compound that is presented according to Example EL22 is reacted, and after working-up and purification, 65.9 mg (65.8 µmol, 60%) of title compound A as well as 19.8 mg (20 µmol, 18%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 1.04 (3H), 1.14 (3H), 1.15 (3H), 1.63 (3H), 0.92-1.85 (23H), 2.10-2.81 (9H), 2.77 (3H), 2.86 (1H), 3.45 (1H), 3.51 (2H), 3.69 (1H), 4.55 (1H), 4.74 (1H), 5.01 (1H), 5.06 (1H), 5.47 (1H), 5.70 (1H), 6.08 (1H), 6.68 (2H), 7.13 (1H), 7.31 (1H), 7.35 (1H), 7.77 (1H), 7.80 (1H), 7.90 (1H) ppm.

Example EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL24a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 271 mg (385 µmol) of the compound that is presented according to Example EL14a is reacted with 1.04 g of the compound that is

presented according to Example L9, and after working-up and purification, 193 mg (193 μmol, 50%) of the title compound is isolated.

Example EL24

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 193 mg (193 μmol) of the compound that is presented according to Example EL24a is reacted, and after working-up and purification, 107 mg (120 μmol, 62%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.02 (3H), 1.07 (3H), 1.23 (3H), 0.97-2.13 (8H), 1.71 (3H), 2.28-2.54 (6H), 2.67 (2H), 2.84 (3H), 2.88 (1H), 2.95 (1H), 3.56 (1H), 3.67 (2H), 4.01 (1H), 4.93 (1H), 4.98 (1H), 5.17 (1H), 5.22 (3H), 5.70 (1H), 5.84 (1H), 6.72 (2H), 7.30 (1H), 7.34 (1H), 7.69 (1H), 7.80 (1H), 7.95 (1H), 8.13 (1H) ppm.

Example EL25

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-butanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 102 mg (115 μmol) of the compound that is presented according to Example EL19 is reacted, and after working-up and purification,

65 mg (72 μmol, 63%) of title compound A as well as 3 mg (3.3 μmol, 3%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.23 (3H), 1.31 (3H), 1.10-2.75 (18H), 2.85 (3H), 3.68 (2H), 3.71 (1H), 4.09 (1H), 4.28 (1H), 4.92 (1H), 4.97 (1H), 5.20 (2H), 5.23 (1H), 5.72 (1H), 6.26 (1H), 6.72 (2H), 7.30 (1H), 7.37 (1H), 7.68 (1H), 7.83 (1H), 7.98 (1H), 8.13 (1H) ppm.

Example EL26

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL26a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 273 mg (387 μmol) of the compound that is presented according to Example EL14a is reacted with 1.12 g of the compound that is presented according to Example L10, and after working-up and purification, 69 mg (67 μmol, 17%) of the title compound is isolated.

Example EL26

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 69 mg (67 μmol) of the compound that is presented according to Example EL26a is reacted, and after working-up and purification, 26 mg (28 μmol, 42%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 0.93 (3H), 0.95 (3H), 1.16 (3H), 1.60 (3H), 0.98-2.61 (20H), 2.73 (3H), 2.77 (1H), 3.45 (3H), 3.83 (1H), 4.05 (1H), 4.83 (1H), 4.88 (1H), 5.05 (1H), 5.13 (3H), 5.62 (1H), 5.74 (1H), 6.61 (2H), 7.16 (1H), 7.26 (1H), 7.60 (1H), 7.70 (1H), 7.88 (1H), 8.03 (1H) ppm.

Example EL27

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-hexanoic acid 4-(1R,3S,7S,10R,11S,12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 38 mg (41 μmol) of the compound that is presented according to Example EL19 is reacted, and after working-up and purification, 14 mg (15 μmol, 37%) of title compound A as well as 2 mg (2 μmol, 5%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.96 (3H), 1.03 (3H), 1.08-1.86 (13H), 1.23 (3H), 1.30 (3H), 2.16 (2H), 2.23-2.78 (7H), 2.83 (3H), 3.54 (2H), 3.71 (1H), 4.09 (1H), 4.27

(1H), 4.91 (1H), 4.96 (1H), 5.21 (3H), 5.72 (1H), 6.25 (1H), 6.69 (2H), 7.23 (1H), 7.36 (1H), 7.67 (1H), 7.82 (1H), 7.96 (1H), 8.11 (1H) ppm.

Example EL28

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Example EL28a

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-(*tert*-butyl-dimethyl-silanyloxy)-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL12b, 273 mg (387 µmol) of the compound that is presented according to Example EL14a is reacted with 1.34 g of the compound that is presented according to Example L11, and after working-up and purification, 196 mg (178 µmol, 46%) of the title compound is isolated.

Example EL28

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(4S,7R,8S,9S,13Z,16S)-[7-allyl-4-hydroxy-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-2,6-dioxo-oxacyclohexadec-13-en-8-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example EL1, 196 mg (178 µmol) of the compound that is presented according to Example EL28a is reacted, and after working-up and purification, 100 mg (101 µmol, 57%) of the title compound is isolated.

^{1}H-NMR ($CDCl_3$): δ = 1.03 (3H), 1.06 (3H), 1.23 (3H), 1.70 (3H), 0.99-1.81 (21H), 1.91 (1H), 2.27-2.53 (6H), 2.63 (2H), 2.83 (3H), 2.88 (1H), 2.95 (1H), 3.51 (2H), 3.56 (1H), 4.00 (1H), 4.92 (1H), 4.98 (1H), 5.13-5.26 (4H), 5.71 (1H), 5.83 (1H), 6.68 (2H), 7.23 (1H), 7.34 (1H), 7.67 (1H), 7.79 (1H), 7.95 (1H), 8.13 (1H) ppm.

Example EL29

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (A) and 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-undecanoic acid 4-(1R,3S,7S,10R,11S, 12S,16S)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester (B)

Analogously to Example EL2, 100 mg (101 μmol) of the compound that is presented according to Example EL19 is reacted, and after working-up and purification, 21 mg (21 μmol, 21%) of title compound A as well as 2 mg (2 μmol, 2%) of title compound B are isolated.

^{1}H-NMR ($CDCl_3$) of A: δ = 0.97 (3H), 1.04 (3H), 1.23 (3H), 0.84-1.84 (24H), 1.71 (3H), 2.15 (2H), 2.23-2.68 (5H), 2.71 (1H), 2.83 (3H), 3.50 (2H), 3.71 (1H), 4.09 (1H), 4.27 (1H), 4.91 (1H), 4.96 (1H), 5.19 (2H), 5.23 (1H), 5.72 (1H), 6.26 (1H), 6.68 (2H), 7.23 (1H), 7.36 (1H), 7.66 (1H), 7.83 (1H), 7.97 (1H), 8.12 (1H) ppm.

Examples of the Synthesis of Effector-Linker Recognition Units (ELE)

Example ELE1

[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

Example ELE1a

Reduction of an Antibody Fragment with Terminal Cysteine

A single-strand protein that consists of the variable domains of the heavy and light antibody chains (single-chain Fv, scFv) of the amino acid sequence EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWV RQAPGKGLEWVSSISGSSGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT AVYYCAKPFPYFDYWGQGTLVTVSSGDGSSGGSGGASEIVLTQSPGTLSLSPGE RATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYYASSRATGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQTGRIPPTFGQGTKVEIKGGGCA, which specifically recognizes the fibronectin domain B (ED-B) and is referred to as AP39, is used for coupling after reduction of the c-terminal cysteine.

For reduction, the solution of 661 µg of tri(2-carboxyethyl)phosphine-hydrochloride in 236 µl of PBS is mixed with the solution of 1.54 mg of AP39 in 1.12 ml of PBS, and it is incubated for 1.5 hours at 25°C. Desalination is done with a pre-equilibrated NAP-5 column at a concentration of 450 µl of AP39r and 50 µl of PBS. After elution with 1 ml of PBS, the reduced antibody fragment AP39r is isolated in a concentration of 0.7 mg/ml.

Example ELE1

(1S,3S,7S(3RS),10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester

22.5 µl of a 1.38 mmol solution of effector-linker conjugate A in DMSO, presented according to Example EL2, is added to 400 µl of the solution, presented according to Example ELE1a, of the reduced antibody fragment, mixed with 77.5 µl of PBS and incubated at 25°C for 1 hour. Desalination is done with a pre-equilibrated NAP5 column at a concentration of 500 µl of the reaction solution. After elution with PBS, the solution of the title compound is isolated The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26203.1 m/z (exp.): 26218 ± 20

Example ELE2

(1S,3S,7S(3RS),10R,11S,12S,16R)-[5-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL4, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26231.2 m/z (exp.): 26236 ± 20

Example ELE3

(1S,3S,7S(3RS),10R,11S,12S,16R)-[10-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-decyl]-carbamic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-7-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL6, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26301.4 m/z (exp.): 26303 ± 20

Example ELE4

(1S,3S,7S,10R,11S(3RS),12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL8, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26203.2 m/z (exp.): 26206 ± 20

Example ELE5

(1S,3S,7S,10R,11S(3RS),12S,16R)-[5-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-pentyl]-carbamic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadec-11-yl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL10, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26231.2 m/z (exp.): 26225 ± 20

Example ELE6

(1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-7-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester (A) and (1S,3S(E),7S,10R,11S,12S,16R)-[3-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-propyl]-carbamic acid-11-[3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propylcarbamoyloxy]-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester (B)

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with the effector-linker conjugate that is presented according to Example EL11, and the solution of the title compounds is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26347.3 m/z (exp.): 26358 ± 20

Example ELE7

(1S,3S(E),7S,10R,11S,12S,16R)-*N*-[1-({4-[2-(7,11-Dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl}-carbamoyl)-ethyl]-3-(AP39r)-disulfanyl-*N*-methyl-propionamide

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL16, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26173 m/z (exp.): 26174 ± 20

Example ELE8

(1S,3S(E),7S,10R,11S,12S,16R)-2-[Methyl-(3-(AP39r)-disulfanyl-propionyl)-amino]-propionic acid-4-[2-(7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-3-yl)-propenyl]-thiazol-2-ylmethyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL17, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26174 m/z (exp.): 26163 ± 20

Example ELE9

(1S,3S,7S,10R,11S,12S,16R)-Carboxylic acid-10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL13, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26238 m/z (exp.): 26224 ± 20

Example ELE10

(1S,3S,7S,10R,11S,12S,16R)-Carboxylic acid-10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yl ester 4-(3-(AP39r)-sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL15, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26238 m/z (exp.): 26243 ± 20

Example ELE11

4-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-11-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-

5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-7-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL19, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26383 m/z (exp.): 26377 ± 20

Example ELE12

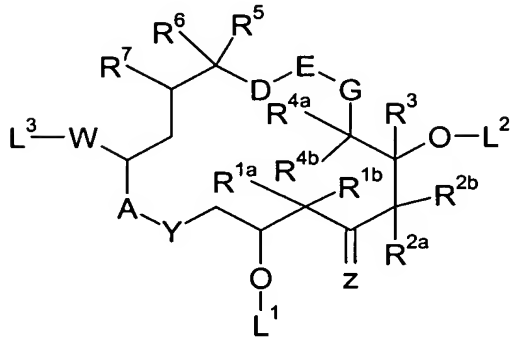
4-(3-(AP39r)-Sulfanyl-2,5-dioxo-pyrrolidin-1-yl)-butanoic acid 4-(1S,3S,7S,10R,11S,12S,16R)-[10-allyl-7-hydroxy-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-5,9-dioxo-4,17-dioxa-bicyclo[14.1.0]heptadec-11-yloxycarbonyloxymethyl]-2-nitro-phenyl ester

Analogously to Example ELE1, the antibody fragment that is reduced according to Example ELE1a is reacted with effector-linker conjugate A that is presented according to Example EL25, and the solution of the title compound is isolated. The dilution factor relative to the antibody fragment is approximately 2.5.

m/z (Cld.): 26383 m/z (exp.): 26381 ± 20

Claims

1. Effector conjugate of general formula (I):



I,

in which

R^{1a}, R^{1b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_m$ group, in which m is 2 to 5,

R^{2a}, R^{2b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_n$ group, in which n is 2 to 5, or C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 is hydrogen, C_1-C_{10} alkyl, aryl or aralkyl, and

R^{4a}, R^{4b}, independently of one another, are hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, or together a $-(CH_2)_p$ group, in which p is 2 to 5,

R^5 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, CO_2H, CO_2alkyl, CH_2OH, CH_2Oalkyl, CH_2Oacyl, CN, CH_2NH_2, CH_2N(alkyl, acyl)$_{1,2}$, or CH_2Hal,

Hal is a halogen atom,

R^6, R^7 in each case are hydrogen, or together an additional bond, or together an oxygen atom, or together an NH group, or together an N-alkyl group, or

together a CH_2 group, and

G is an oxygen atom or CH_2,

D-E is a group H_2C-CH_2, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH_2, CH_2-CH(OH),  , O-CH_2, or, if G represents a CH_2 group, D-E is CH_2-O,

W is a group C(=X)R^8, or a bicyclic or tricyclic aromatic or heteroaromatic radical,

L^3 is hydrogen, or, if a radical in W contains a hydroxyl group, forms a group O-L^4 with the latter, or, if a radical in W contains an amino group, forms a group NR^{25}-L^4 with the latter,

R^{25} is hydrogen or C_1-C_{10} alkyl,

X is an oxygen atom, or two OR^{20} groups, or a C_2-C_{10} alkylenedioxy group that should be straight-chain or branched, or H/OR^9, or a $CR^{10}R^{11}$ group,

R^8 is hydrogen, C_1-C_{10} alkyl, aryl, aralkyl, halogen or CN, and

R^9 is hydrogen or a protective group PG^X,

R^{10}, R^{11}, in each case independently of one another, are hydrogen, C_1-C_{20} alkyl, aryl, aralkyl, or together with a methylene carbon atom form a 5- to 7-membered carbocyclic ring,

Z can represent oxygen or H/OR^{12},

R^{12} can represent hydrogen or a protective group PG^Z,

A-Y can represent a group O-C(=O), O-CH_2, CH_2-C(=O), NR^{21}-C(=O) or NR^{21}-SO_2,

R^{20} can represent C_1-C_{20} alkyl,

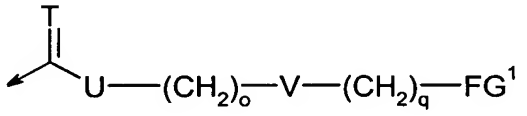
R^{21} can represent a hydrogen atom or C_1-C_{10} alkyl,

PG^X, PG^Y, and PG^Z can represent a protective group PG, and

L^1, L^2, and L^4, independently of one another, can represent hydrogen, a group C(=O)Cl, a group C(=S)Cl, a group PG^Y or a linker of general formula (III) or (IV);

provided that at least one substituent L^1, L^2 or L^4 represents a linker of general formula (III) or (IV);

the linker of general formula (III) has the following structure,



III,

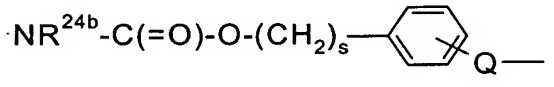
in which

T can represent oxygen or sulfur,

U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=O)-, O-C(=O)-CHR^{22}-NR^{23}-C(=S)-, CHR^{22}-NR^{23}-C(=S)- or NR^{24a},

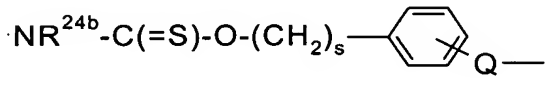
o can represent 0 to15,

V can represent a bond, aryl, a group



,

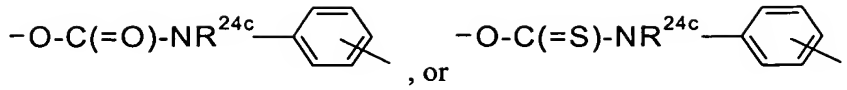
or a group



,

s can represent 0 to 4,

Q can represent a bond, O-C(=O)-NR^{24c}, O-C(=S)-NR^{24c},

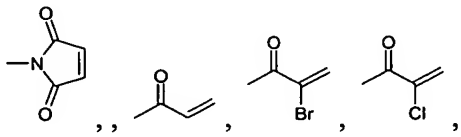


R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen or C_1-C_{10} alkyl,

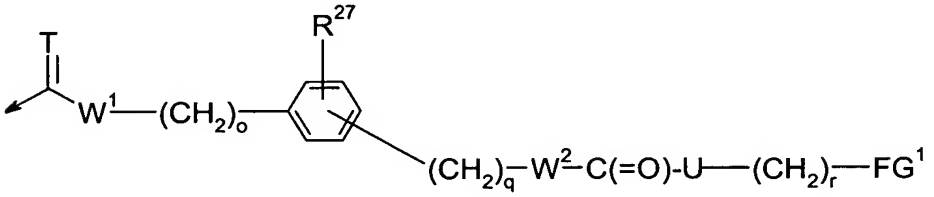
R^{24a}, R^{24b}, and R^{24c}, independently of one another, can represent hydrogen or C_1-C_{10} alkyl,

q can represent 0 to 15,

FG^1 can represent C_1-C_{10} alkyl-S_3 , 


, or CO_2H; and

the linker of general formula (IV) has the following structure,



IV,

in which

T can represent oxygen or sulfur,

W^1, W^2 are the same or different and can represent oxygen or NR^{24a},

o can represent 0 to 5,

R^{24a} can represent hydrogen or C_1-C_{10} alkyl,

R^{27} can represent halogen, CN, NO_2, CO_2R^{28}, or OR^{28},

R^{28} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

q can represent 0 to 5,

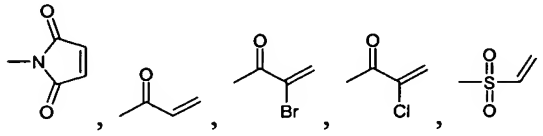
U can represent oxygen, CHR^{22}, CHR^{22}-NR^{23}-C(=O)-, CHR^{22}-NR^{23}-C(=S)- or C_1-C_{20} alkyl,

R^{22} can represent hydrogen, C_1-C_{10} alkyl, aryl or aralkyl,

R^{23} can represent hydrogen or C_1-C_{10} alkyl,

r can represent 0 to 20,

FG^1 can represent C_1-C_{10} alkyl-S_3,



, or CO_2H,

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

2. Effector conjugate according to claim 1, whereby:

A-Y represents O-C(=O) or NR^{21}-C(=O),

D-E represents an H_2C-CH_2 group,

G represents a CH_2 group,

Z represents an oxygen atom,

R^{1a}, R^{1b} in each case represent C_1-C_{10} alkyl or together a $-(CH_2)_p$ group with p equal to 2 or 3 or 4,

R^{2a}, R^{2b}, independently of one another, represent hydrogen, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkinyl,

R^3 represents hydrogen,

R^{4a}, R^{4b}, independently of one another, represent hydrogen or C_1-C_{10} alkyl;

R^5 represents hydrogen, or C_1-C_4 alkyl or CH_2OH or CH_2NH_2 or $CH_2N(alkyl, acyl)_{1,2}$ or CH_2Hal,

R^6 and R^7 together represent an additional bond or together an NH group, or

together an N-alkyl group, or together a CH_2 group, or together an oxygen atom,

W represents a group $C(=X)R^8$ or a 2-methylbenzothiazol-5-yl radical or a 2-methylbenzoxazol-5-yl radical or a quinolin-7-yl radical or a 2-aminomethylbenzothiazol-5-yl radical or a 2-hydroxymethylbenzothiazol-5-yl radical or a 2-aminomethyl-benzoxazol-5-yl radical or a 2-hydroxymethylbenzoxazol-5-yl radical,

X represents a $CR^{10}R^{11}$ group,

R^8 represents hydrogen or C_1-C_4 alkyl or a fluorine atom or a chlorine atom or a bromine atom,

R^{10}/R^{11} represent hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl or hydrogen/2-methyloxazol-4-yl or hydrogen/2-aminomethylthiazol-4-yl or hydrogen/2-aminomethyloxazol-4-yl or hydrogen/2-hydroxymethylthiazol-4-yl or hydrogen/2-hydroxymethyloxazol-4-yl.

3. Effector conjugate according to claim 1 or 2, whereby the effector building block is selected from the group that consists of:

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-methyl-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-methyl-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-methyl-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-fluoro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-fluoro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-fluoro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(Z))-16-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[1-chloro-2-(2-methyl-oxazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-oxazol-4-yl)-1-chloro-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(Z),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-oxazol-4-yl)-1-chloro-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-methyl-thiazol-4-yl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S(E))-16-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-methyl-thiazol-4-yl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-[2-(2-hydroxymethyl-thiazol-4-yl)-vinyl]-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-3-[2-(2-Aminomethyl-thiazol-4-yl)-vinyl]-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-[2-(2-pyridyl)-vinyl]-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-[2-(2-pyridyl)-vinyl]-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzothiazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzothiazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzothiazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzothiazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzothiazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzothiazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-5,5,7,9,13-pentamethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-ethyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-ethyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-propyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-propyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-propyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-propyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-butyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-butyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-butyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-butyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-allyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-allyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-allyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-allyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-prop-2-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-prop-2-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-enyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-enyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-16-(2-methyl-benzoxazol-5-yl)-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-4,8-Dihydroxy-16-(2-hydroxymethyl-benzoxazol-5-yl)-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(4S,7R,8S,9S,13Z,16S)-16-(2-Aminomethyl-benzoxazol-5-yl)-4,8-dihydroxy-7-but-3-inyl-5,5,9,13-tetramethyl-oxacyclohexadec-13-ene-2,6-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-3-(2-methyl-benzoxazol-5-yl)-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-hydroxymethyl-benzoxazol-5-yl)-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione;

(1S,3S,7S,10R,11S,12S,16R)-3-(2-Aminomethyl-benzoxazol-5-yl)-7,11-dihydroxy-10-but-3-inyl-8,8,12,16-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione,

whereby the hydrogen atoms in the above-mentioned effector building blocks are replaced in the positions indicated in formula (I) by radicals L^1-L^3.

4. Effector conjugate according to one of claims 1-3, whereby the linker is selected from the group that consists of the compounds of general formula (III), whereby

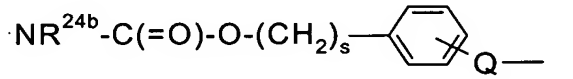
V represents a bond or an aryl radical,

o is zero, and

T is an oxygen atom.

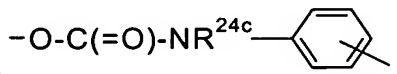
5. Effector conjugate according to one of claims 1-3, whereby the linker is selected from the group that consists of the compounds of general formula (III), whereby

V represents a bond or an aryl radical or a group



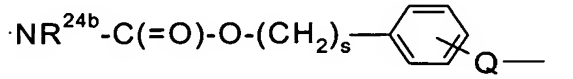
,

o is 0 to 4, and

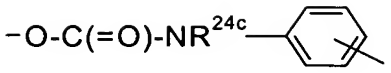
Q is a bond or a group  .

6. Effector conjugate according to claim 5, whereby

V is a bond or a group



,

Q is a bond or a group  ,

o is 0, 2 or 3,

s is 1, and

T is an oxygen atom.

7. Effector conjugate according to one of claims 1-3, whereby the linker is selected from the group that consists of compounds of general formula (IV), whereby

o is 0 to 4, and

q is 0 to 3.

8. Effector conjugate according to claim 7, whereby

o is 0, 2 or 3,

W^1 is oxygen,

q is 0,

R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl,

R^{23} is hydrogen or C_1-C_3 alkyl,

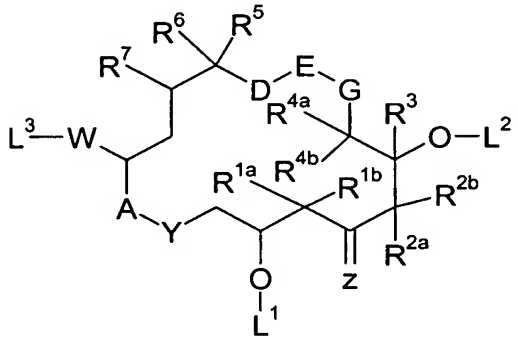
R^{24a} is hydrogen or C_1-C_3 alkyl,

R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28},

R^{28} is hydrogen or C_1-C_5 alkyl, and

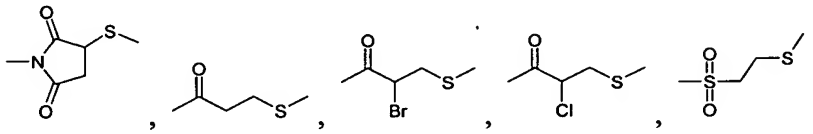
U is oxygen, CHR^{22}, or CHR^{22}-NR^{23}-C(=O)-.

9. Effector recognition unit conjugate of general formula (I),



I,

whereby the substituents therein have the meanings that are mentioned in claim 1, but at least one group FG^1 is replaced by a group FG^{2a} or FG^{2b}, whereby FG^{2a} or FG^{2b} can have the following meanings:

FG^{2a}: -S-S-, 

FG^{2b}: -CONH-

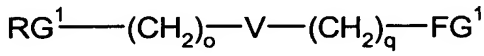
and whereby a recognition unit is conjugated via a sulfur atom with the group FG^{2a} or via an amide function with group FG^{2b}; whereby the recognition unit is selected from the group that consists of peptides, soluble receptors, cytokines, lymphokines, aptamers, spiegelmers, recombinant proteins, new framework structures, monoclonal antibodies and fragments of monoclonal antibodies;

as a uniform isomer or a mixture of different isomers and/or as a pharmaceutically acceptable salt thereof.

10. Effector recognition unit conjugate according to claim 9, whereby the conjugate contains more than one recognition unit, and whereby the recognition units are identical.

11. Effector recognition unit conjugate according to claim 9 or 10, whereby the recognition unit is an antibody, or an antigen-binding fragment thereof, which is specific for an antigen that is selected from the group that consists of the antigens that are cited in Table 1, as well as CD19, CD20, CD40, CD22, CD25, CD5, CD52, CD10, CD2, CD7, CD33, CD38, CD40, CD72, CD4, CD21, CD37, CD30, VCAM, CD31, ELAM, endoglin, VEGFRI/II, $\alpha_v\beta_3$, Tie1/2, TES23 (CD44ex6), phosphatidylserine, PSMA, VEGFR/VEGF complex and ED-B-fibronectin.

12. Linker of general formula (III^1):

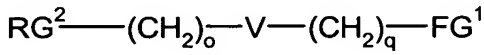


$$RG^1\text{---}(CH_2)_o\text{---}V\text{---}(CH_2)_q\text{---}FG^1 \qquad \mathbf{III^1},$$

in which

RG^1 is an O=C=N group or an S=C=N group, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (III^2):

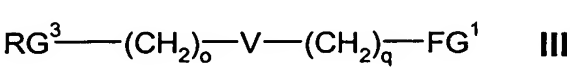


$$RG^2\text{---}(CH_2)_o\text{---}V\text{---}(CH_2)_q\text{---}FG^1 \qquad \mathbf{III^2},$$

in which

RG^2 is a Hal-C(=T)-CHR^{22} group, or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, whereby R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (III^3):



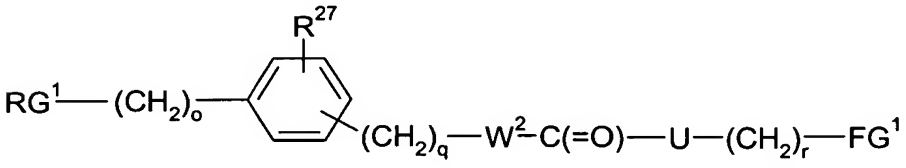
$$RG^3\text{---}(CH_2)_o\text{---}V\text{---}(CH_2)_q\text{---}FG^1 \qquad \mathbf{III^3},$$

in which

RG^3 is an OH group, or an NHR^{24a} group, or a COOH group, and o, V, q and FG^1 have the meanings that are mentioned in claim 1;

but with the condition that the compound 1-(4-amino-phenyl)-pyrrole-2,5-dione is not included.

13. Linker of general formula (IV^1):



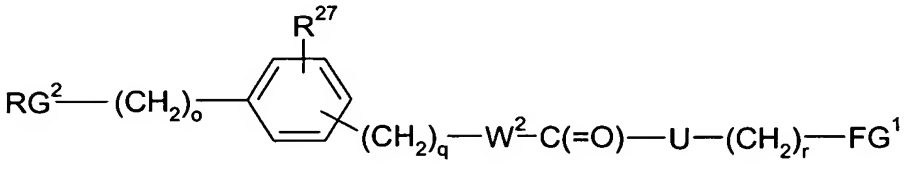
IV¹

,

in which

RG^1 is an O=C=N group or an S=C=N group, and o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (IV^2):



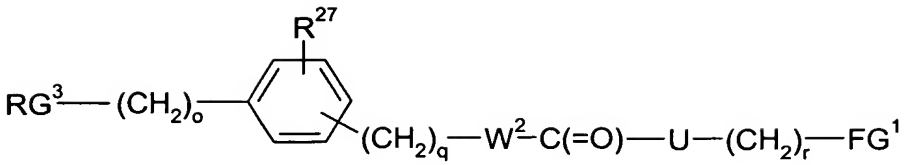
IV²

,

in which

RG^2 is a Hal-C(=T)-CHR^{22} group, or a Hal-C(=T)-CHR^{22}-NR^{23}-C(=T) group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22} group, or an R^{26}-C(=O)-O-C(=T)-CHR^{22}-NR^{23}-C(=T) group, whereby R^{26} is C_1-C_{10} alkyl, aryl, or aralkyl, and R^{22}, R^{23}, T, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1;

or linker of general formula (IV^3):



IV³

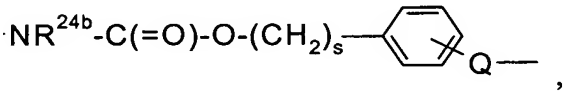
in which

RG^3 is an OH group or an NHR^{24a} group or a COOH group, and R^{24}, o, q, r, W^2, R^{27}, U and FG^1 have the meanings that are mentioned in claim 1.

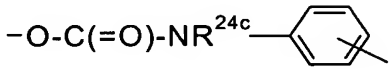
14. Linker according to claim 12, whereby V represents a bond or an aryl radical, o is equal to zero, and T is an oxygen atom.

15. Linker according to claim 12, whereby

V represents a bond or an aryl radical or a group

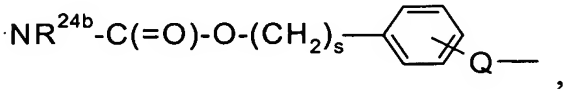


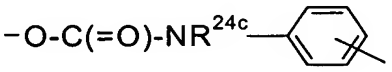
o is 0 to 4, and

Q is a bond or a group  .

16. Linker according to claim 15, whereby

V is a bond or a group



Q is a bond or a group  ,

o is 0, 2 or 3,

s is 1, and

T is an oxygen atom.

17. Linker according to claim 13, whereby

o is 0 to 4, and

q is 0 to 3.

18. Linker according to claim 17, whereby

o is 0, 2 or 3,

W^1 is oxygen,

q is 0,

R^{22} is hydrogen, C_1-C_3 alkyl or aralkyl,

R^{23} is hydrogen or C_1-C_3 alkyl,

R^{24a} is hydrogen or C_1-C_3 alkyl,

R^{27} is fluorine, chlorine, CN, NO_2, CO_2R^{28} or OR^{28},

R^{28} is hydrogen, or C_1-C_5 alkyl, and

U is oxygen, CHR^{22}, or CHR^{22}-NR^{23}-C(=O)-.

19. Process for the production of effector conjugates according to one of claims 1-8, whereby a compound of general formula (I), whereby the substituents have the meanings that are mentioned in claim 1, but the condition that at least one substituent L^1, L^2 or L^4 represent a linker of general formula (III) or (IV) need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(=S)Cl, is reacted with a linker that is selected from the group that consists of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3), as described in claims 12 to 18.

20. Process for the production of effector recognition unit conjugates according to one of claims 9 to 11, whereby an effector conjugate according to one of claims 1-8 is reacted with at least one recognition unit, as defined in claims 9 and 11.

21. Use of a compound of general formula (I), whereby the substituents have the meanings that are mentioned in claim 1, but the condition that at least one substituent L^1,

L^2 or L^4 represent a linker of general formula (III) or (IV) need not be met, and at least one substituent L^1, L^2 or L^4 represents hydrogen, a group C(=O)Cl, or a group C(=S)Cl, in a process according to claim 19.

22. Use of a compound of general formula (I) for the production of an effector recognition unit conjugate according to claims 9 to 11.

23. Use of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3) in a process according to claim 19.

24. Use of a linker of general formula (III^1), (III^2), (III^3), (IV^1), (IV^2) or (IV^3) for the production of an effector recognition unit conjugate according to one of claims 9 to 11.

25. Use of a recognition unit, as defined in claim 9 or 11, in a process according to claim 20.

26. Effector recognition unit conjugate according to one of claims 9 to 11 for use as a medication.

27. Effector recognition unit conjugate according to one of claims 9 to 11 for use as a medication for treating diseases that are associated with proliferative processes.

28. Effector recognition unit conjugate according to one of claims 9 to 11 for use as a medication for treating a disease that is selected from the group that consists of tumors, inflammatory diseases, neurodegenerative diseases, angiogenesis-associated diseases, multiple sclerosis, Alzheimer's disease, and rheumatoid arthritis.

Abstract:

Conjugates of epothilones and epothilone derivatives (as effectors) with suitable biomolecules (as recognition units) are described. Their production is carried out by the effectors being reacted with suitable linkers, and the compounds that are produced are conjugated to the recognition units. The pharmaceutical use of the conjugates for treating proliferative or angiogenesis-associated processes is described.